BLUE

Safety Assessment of Panax spp. Root-Derived Ingredients as Used in Cosmetics

CIR EXPERT PANEL MEETING

SEPTEMBER 10-11, 2012

Cosmetic Ingredient Review
Commitment . . . Credibility
Since 1976

August 17, 2012

MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Subject: Draft Final Report for panax ginseng root and other ginseng root derived ingredients used in cosmetics

The Cosmetic Ingredient Review (CIR) Expert Panel issued a tentative report in June, 2012 with the conclusion of safe in the present practices of use and concentration.

No new data have been submitted by industry. All comments received after the Panel meeting has been addressed in this report.

The Panel should review the Draft Final Report and determine if the abstract, discussion, and conclusion reflect the Panel's thinking.

The Panel should issue a Final Report.

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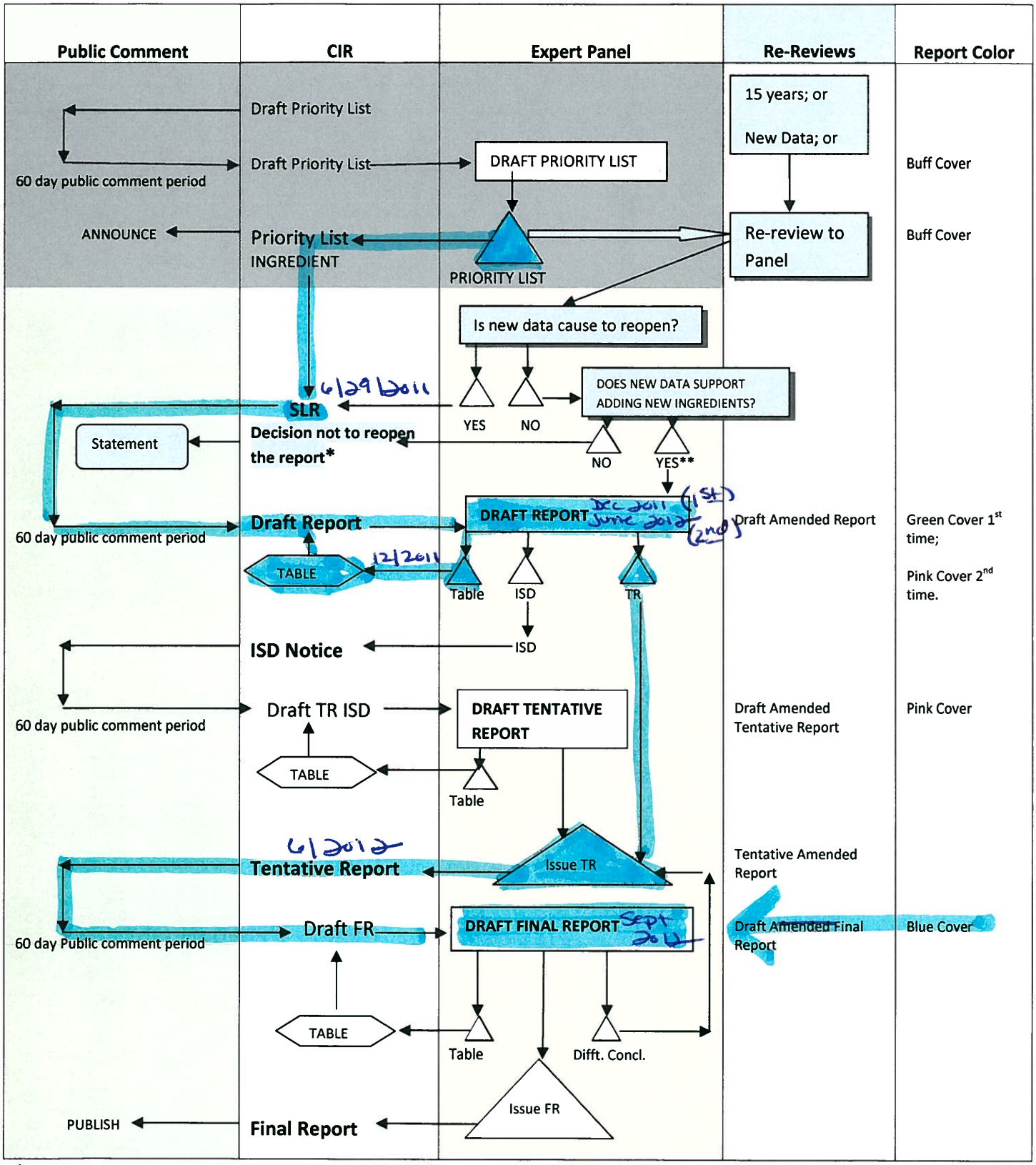
Panel Scoping Report Extract

SAFETY ASSESSMENT FLOW CHART

Sept 2012



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

△ Expert Panel Decision

▭ Document for Panel Review

⇨ Option for Re-review

History of Panax Ginseng Root

June, 2010 – It was announced that ginseng root is on the priority list.

June, 2011 – SLR was posted for public comment.

July, 2011 – The Council requested that the Draft Report be delayed until December, 2011 so that the use survey may be completed. This request was granted.

December, 2011 – The Panel examined the Draft Report. The Panel was concerned about a case report suggesting phytoestrogenic effects. Since there was no other data, the report was tabled so that further research could be conducted.

June, 2012 – The Panel was satisfied that there were no possible phytoestrogenic effects. A safe as used conclusion was issued.

September, 2012 – The Panel should issue a Final Report.

Ginseng Data Profile for September, 2012. Writer - Lillian Becker

	ADME			Acute toxicity			Repeated dose toxicity			Irritation			Sensitization					
	Dermal Penetration	Log K_{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Panx ginseng root extract			X	X			X	X				X		X	X	X	X	X
Hydrolyzed ginseng root																		
Hydrolyzed ginseng root extract																		
Hydrolyzed ginseng saponins											X	X			X	X		
Panax ginseng root			X															
Panax ginseng root powder																X		
Panax ginseng root water																		
Panax ginseng root oil																		
Panax ginseng root protoplast																		
Panax japonicas root extract																		
Panax notoginseng root			X															
Panax notoginseng root powder																X		
Panax quinquefolium root extract			X				X							X		X		

Search Strategy for Ginseng Root Ingredients

Terms	**USDA National Agriculture Library** (6/10011)	ECETOC (1/2011)	SCCP & SCCN (1/2011	IUCLID (1/2011)	IARC (1/2011)	HPVIS (1,2/2011)	Dogpile (1,2/2011)
Gingeng; ginseng AND extraction after 1980	1200+ hits; no hits	0	0	0	0		
CAS Nos & INCI names						Hits on P. tetra C5-10 & C5-9 acid esters	
CAS Nos.							A few MSDS

Search for Endocrine/Estrogen/Hormonal Activity		
Search Term	**SciFinder**	**PubMed**
Does ginseng root have estrogen activity	7 hits, 3 possibly useful	
Adverse Effects from Ginseng	49 hits, 8 possibly useful	
Ginseng hormonal activity	26 hits, 5 possibly useful – several duplicates.	
Estrogen activity in ginseng	54 hits	
Panax ginseng AND estrogen		47 hits, 6 possibly useful (overlap with SciFinder)
Ginseng endocrine activity	5 hits, 5 possibly useful	

Transcript

Transcripts for Ginseng Root Ingredients
June, 2012 Meeting

Dr. Belsito's Team

DR. BELSITO: Any other comments on the priority list? If not, I guess we get to move to our first botanical.

So this is panax ginseng root derived ingredients. There are a total of 13 that are listed in your panel book. The last time we looked at this we sort of did a temporary timeout to allow Lillian to look at the phytoestrogenic activity in this group and it's similar to how we address the activity in the PEG soy sterile safety assessment that has been updated in this report. And I'd like to make --

DR. BRESLAWEC: I'm sorry. Before we go into this can I make a correction to the statement I made previously on the insufficient data? The category is safety not substantiated. So if something is insufficient and it doesn't -- we don't get any additional data, it goes into a new category called safety not substantiated where previous insufficient data go. It's a different category than Unsafe; practically it has the same implications. Thank you.

DR. BELSITO: Okay. Thanks, Halyna. So if anyone feels that that needs to be beefed up anymore, let us know and Lillian can certainly give you additional data from the PEG soy sterile report. If everyone is comfortable with the phytoestrogenic effects in this report, then we still have the issue of the pulegone levels that we discussed in December. Now, it has been noted as a botanical, the final concentration of this is in products typically quite low. I think the highest is 0.5 percent in a leave-on and it's not quite clear what that leave-on is. It's listed just as a dermal contact and that's for the ginseng root extract.

And then I guess just to follow up on my prior comment, when we're limiting impurity levels these botanicals are being added 5, 6, 7, 8 to an individual ingredient and how do we deal with that I presume someplace in the discussion. That if it were to be used in combination with other ingredients that could contain pulegone, we would assume that the final level would be at a certain amount.

So having said all that I thought it was safe as used. I didn't really think the endocrine disruption area needed to be beefed up at all. I thought it was fairly well done. I just struggled with the idea of how to restrict pulegone because if we say let's limit to 1 percent and the highest is 0.5 in a leave-on, then that's 0.005 percent in a finished product. And is that the level we're going to -- because once you set a level for pulegone that will be used based off of this report, presumably that would be the level we would set for every other botanical that has potentially pulegone but it shouldn't contain more than 0.005 percent in the finished leave-on product.

So that's what I have to say and I want to hear from you guys.

DR. SNYDER: Well, I think in that lies the problem. I think we would probably have to have some language in there about the level and the final product. Would that then account for this botanical being one component of a final product?

DR. BELSITO: Yeah, I mean, I think that's what we need to do. But then do we have the data to support 0.005 percent pulegone as being safe?

MS. BECKER: You base this level -- am I on? Thanks. You based this level on the peppermint assessment and we just transferred the information here and applied it to the ginseng. So if you want to tie in the peppermint saying that the two of them together cannot go over or some kind of way like that, some kind of way that you show the combination should never go over.

DR. BELSITO: See, I think the problem that I'm having is that we've never thought about these as being additive as a result of having more than one botanical in a product.

And we did that based upon peppermint presumably because it was looked at at a certain percentage and we back calculated. So we would have to go back and look at what was the percentage of peppermint oil or whatever it was of peppermint that contained pulegone that we said was okay because just because it was less than 1 percent in peppermint, peppermint may be used at only 0.00001 percent max in the finished product. And I don't know that. I mean, you know, it's something that I really started, you know, thinking about as I was looking at the last two botanicals that we were asked to re-review and then suddenly thinking, okay, yeah, through thujone quercetin, you know, we're seeing these in a number of botanicals and we need to start worrying about additive affects. So I really didn't go back and look at where this less than 1 percent level came from.

DR. BERGFELD: Can't we just put that in the discussion that it should have no additive effect? I mean, some general statement? Why do we have to put a number on it?

DR. BELSITO: Well, because I think that as we look at botanicals and we're concerned about impurity levels, like quercetin and thujone and pulegone, you can't simply put a level on a specific botanical product because you read the labels and I won't do the scientific names but on a number of products you go down and there's sunflower and there's calendula and there's chamomile and there's rosemary and there's thyme and, you know, and the list goes on and on and on. And so if you were to limit thujone and rosemary, you know, and limit it in thyme, by the time you add all of these botanicals that are put into a given lotion you could have levels much higher than you ever anticipated in the finished product.

MS. BECKER: I think we can address that in the discussion. If it's used alone, this is the limit. If you're combining it with other botanicals that this may be an issue, the total across the board may not be over this number.

DR. BELSITO: But that's my point. We've so far, as far as I can recollect, for every single contaminate we were concerned about, relied on dermal studies that suggested that there were no issues when peppermint oil used at a certain percentage that contained a potential certain percentage of the contaminant was put onto the skin. We've never, as far as I know, looked at a study that allows us to say, you know, thujone is a non-issue when it is present up to a certain percentage. We don't have that data to set the limits. It may be out there. I have never seen the data that allows me to set the limits on those particular components of botanicals that we're concerned about.

DR. KLAASSEN: We need to go back to the peppermint. You know, if this pulegone is really a problem, I don't remember what the whole issue was in how we came to that in peppermint. Is that the only place that we've come across this? And what was the data on it? You know, how much of a problem really was it? I don't recall.

DR. BERGFELD: And are there other studies about pulegone and setting limits on risk assessment? I mean, we have an upper threshold on it.

DR. KLAASSEN: I don't recall.

DR. BELSITO: You know, as far as I know, we've, again, all of our safety data as we've looked at this has been use of particular botanical at a certain concentration and a dermal study or some study where it had this percentage of this contaminant and it was fine. So I don't recollect ever looking, and I think the three ones that we've dealt with are thujone, quercetin and pulegone. And I don't recall ever looking specifically at those three chemicals and coming up with a level, for lack of a better word, a TTC for those chemicals that would allow us to say in a finished product regardless of the sourcing, chemical X should not exceed this amount. And therein lies my dilemma as we -- you know, it's just like, you know, when we do, you know, should not be formulated to form nitrosa compounds. So, you know, this is now, you know, should not be formulated so that a chemical is above a certain level. But we don't have --

DR. BERGFELD: Or to produce safety hazard to the user. I mean, there is

other language you could use.

DR. BELSITO: I guess. But then in essence we would be asking industry to do the type of data that we're looking for. Exactly how high can you go with these chemicals where they're not?

MS. BECKER: Lillian, can you get on Alan's computer and see if we can pull up the peppermint report? Or do you want me to?

DR. BERGFELD: While you're doing that I just have another question that maybe Bart can answer. Most of the testing on the mixture I guess on the root extract is on the first two in the listing on page 1, the panax ginseng root extract. And the second one was on the powder. Now, you have a lot of different extracts from the root and some of them -- I'm not sure they're all the same. And so, but we are not characterizing them. You have a lot there. You have a lot of root extracts. I would think the powder and the root water would be somewhat similar but maybe not. But you have an oil. You have root protoplast. You have japonicas, et cetera, et cetera there. And we've only got two that have been tested - saponins and the root extract, something called panax ginseng root extract are the only two that have been tested or characterized. You're not worried about that? Look at all these ingredients here. Do you feel comfortable with the chemistry for all those?

DR. BELSITO: In Table 4 it goes through the proposed constituents from low to high of the root.

DR. BERGFELD: Yeah, but the question I have of you is that you have only tested two, but are you comfortable with all the others that have been included in that? Are they different?

DR. LIEBLER: So Table 4 I guess it is that provides the detailed description is just for the panax ginseng root extract. And the low and high I guess are a variety of batches that have been analyzed. We don't really have data for the other ingredients like the notoginseng root, for example. So I think the assumption that we would have -- I mean, they are almost certainly different. And then the question is in the absence of data, detailed data on the chemical composition of these, can we make an assessment about their safety? So am I rephrasing your question basically?

DR. BERGFELD: Yeah, I think they're different.

DR. LIEBLER: Yeah.

DR. BERGFELD: I think they're different and we don't have any information and testing on them.

DR. LIEBLER: Yeah.

DR. BERGFELD: But you chemists, I was wondering. You're accepting all that. I'm a clinician.

DR. BELSITO: What we're looking at is all root. The only one is hydrolyzed ginseng saponins which we have the information on what the saponins are from the root extract. So, I mean, I think in this case -- and we also have information on the different genuses or species rather because there's panax, quinquefolium, and panax notoginseng and several others. So we do have that information.

DR. EISENMANN: One more thing, and I don't know how true this is, but the table for the quinquefolium says that the pulegone is in the root essential oil and that's not a cosmetic. The root essential oil of that species is not a cosmetic ingredient. So I'm not sure that that component is necessarily -- not that I'm saying -- I think a project to look at what is a safe level of some components of concerns of plants probably would be a good project but I'm not sure that for this group of ingredients that it's appropriate. One thing that I was a little concerned about is the hydrolyzed ingredients, that they're in this report and that there's a number of hydrolyzed grape ingredients that are not in the grape report. I'm not sure why that was chosen;

why they were in one report and not in the other. But I'm not sure what the hydrolyzed -- what it means by hydrolyzed extract ginseng root extract, what that means.

DR. BELSITO: But wasn't that portion of grape that we didn't include hydrolyzed grape skin?

DR. EISENMANN: Yes, but you've got grape skin itself is in there, so.

DR. BELSITO: Oh, okay.

DR. EISENMANN: So I didn't quite understand the logic of including grape. Including it.

DR. BELSITO: Well, I guess we'll discuss that when we get to grape.

DR. SNYDER: So the one that contains pulegone contaminant is the quinquefolium and this only goes to 0.002 percent. So not 0.5 percent.

DR. EISENMANN: And it's an extract versus the pulegone. The way this is written, Dr. Duke found it went to the oil so I don't know how true that is but that looks like -- so I'm not sure. I mean, I think you should probably set some kind of limit but I'm not sure that that should hold up -- necessarily hold up this report because that's not necessarily -- it doesn't seem like it's a big component of the main ingredient that's being used.

DR. BELSITO: Okay. And Lillian just pointed out that I have to eat my prior words because in the peppermint oil report. We actually did look at two different studies that specifically looked at pulegone and came up -- both studies came up with the no observed adverse effect levels of 20 mg/kg/day and that was in the peppermint report which certainly would allow us to come to some conclusion on pulegone which I guess may not be an issue in this report because in the discussion we can point out that its presence was in an extract that is not considered as a cosmetic ingredient. Just to give you some flavor of how we put it in the discussion -- I'm on the wrong report. Although it may not be an issue for this one but while we have it out, in assessing the safety we were concerned about oral dosing studies that reported cyst-like spaces in the cerebellum. The results of these studies were difficult to interpret, the findings were not consistent among studies, and other lesions appeared to depend upon the pulegone content. No definitive conclusions could be made. A greater NOAEL was reported in a 90-day study using the peppermint oil. And then we went on to talk about the 20 mg/kg/day no effect level of pulegone. So for pulegone at least we have studies suggesting issues with that and I guess we'll have to continue to look as we move to the other ones.

But I guess in this case, I mean, we can point out that the essential oil extract of quinquefolium -- it's the quinquefolius root -- was reported to have pulegone. However, this is not a cosmetic ingredient and the other components or species of ginseng that were used were not reported to have pulegone or something to that effect. So safe as used. Mention of pulegone in the discussion but it's not an ingredient.

Rachel.

MS. WEINTRAUB: One thing I wanted to ask you. The last time you discussed this, whenever it was in March, the question about the estrogenic effect was of great concern and you particularly raised it last time and this time you just sort of mentioned it briefly. I wanted to really explore that and to get a sense of whether the panel is no longer concerned about that, and if so, why.

DR. BERGFELD: We have two negative reproductive studies with PGRE, up to 20 mg/kg. It references 157 and 158.

DR. BELSITO: The reports of the FIDO estrogenic effects were anecdotal and that's pointed out now. And as Paul pointed out, we have two negative repressed studies. So I think those issues have been dissipated by that. Plus, the anecdotal reports dealt with ginseng species that are not used in cosmetic products.

DR. LIEBLER: One other thing is the anecdotal reports are with products that

aren't very well characterized with respect to what was in them, whereas, the studies are with products that are better characterized and there are a couple of references in Table 20 to the in vivo and in vitro studies that referred to the impact of contaminants. Mycotoxin-derived contaminants in producing the hormonally- related effects. And therefore, serving as confounders. So, you know, it's almost impossible to say what was happening in the cases with the anecdotal reports. I think the anecdotal report, the one woman who is the first one in I guess is it Table 19?

DR. BERGFELD: Twenty.

DR. LIEBLER: Or Table 20. Okay, table -- no, no.

DR. BELSITO: Post-menopausal.

DR. LIEBLER: Yeah, the one that Don was referring to the last time when we met. That was Table 20. Oh, you're right. It is Table 20, the Fang Fang ginseng face cream. Yeah. That's a good example of something where there's no information on the contents of the cream. So when we do have data on defined materials then I think they suggest that the estrogenic effects are not significant.

DR. BERGFELD: I'm sorry, I didn't hear how you resolved the differences in the chemical composition of the various botanicals in this listing. You just passed over it and said it was okay?

DR. LIEBLER: Well, we have no data for most of them. I mean, we really have inadequate data for the compounds. Some of the compounds, particularly the ones that aren't in use. And the best data we have are from panax ginseng root extract. Right? That's where we have that big table with all the components from multiple batches. And that's the only one we have much chemical characterization on. We have toxicity data for the panax quinquefolium root extract and for the saponins. The saponins are better characterized chemically. The other root extracts are not; at least we don't have any data on them. So between the relatively low levels of usage of these for what toxicity data we have that's pretty similar that alleviates my concern a little bit. I would like to have much better characterization of botanicals, you know, some type of a chemical profile. But that's obviously not something that we have before us at this point.

DR. BERGFELD: So will you take that up in your discussion as a couple of sentences?

DR. LIEBLER: Yeah.

DR. BELSITO: And I guess this goes back to the, you know, the presentation we just heard. You know, food, medicinal, and we know that aqueous extracts of ginseng have medicinal uses that, you know, so it moves it into a slightly different category as we go down and evaluate it.

DR. LIEBLER: We know more about these in terms of their properties and some asses than we do about their chemical composition. And that's the problem we have with all these botanicals. And as long as we get these ingredient groups that are lumped in that are uncharacterized materials we're going to be in this boat.

DR. BERGFELD: I realize that because we've been dealing with them for several years but since there's been such a presentation on knowing the composition today I would think that it would be prudent for us to do something in the discussion to say why we've allowed them to be in the listing, especially when you talked about the ginseng root oil listing.

DR. LIEBLER: Right. I mean, we can take this up in the discussion, of course. And then there's the question of whether we push back against evaluating the safety of chema of mixtures for which we have very little information about their composition.

DR. BERGFELD: Well, we have the famous Rice document. Ron was an advocate of getting all the chemical compositions for all of those. There are about 25 of them or

30 of them.

DR. BELSITO: It was Ron Shank, not Hill.

MS. WEINTRAUB: I do think this is a really important discussion and it really seems like it's the burden of the manufacturers of the products who are using these things to provide this basic chemical structure information. It seems like if they're using it in their products they should know it.

DR. LIEBLER: The technology exists now to profile these by LC/MS, to provide very informative inventories with ranges of concentration, although maybe not precise measurements but at least useful ranges of concentrations of categories of compounds to do this. You know, if outfits like L'Oreal with reasonably good size analytical laboratories could do this, I don't know what's available in the contract lab space to do this in any kind of a standardized way. But as long as we -- I mean, I think it's possible to do it now technically. It's obviously not happened with panax ginseng root extracts because we don't have the data. So we're left with reasoning from a little bit of chemistry, chemical composition information, and then a patchwork of toxicology results and use concentrations that tend to be low.

Both of those mitigate my concern but I'd like to have the chemistry. And I guess we could raise it in the discussion but is there anything more that we could do to push back on botanical ingredients where we really just don't have composition information, chemical composition information. I counted in the upcoming list of priorities for next year I think five or six botanical ingredients and I assume it would be in the same boat with those.

DR. EISENMANN: Table 9, I mean, some companies are measuring saponin levels. And these were -- it's on page -- Panel Book 46. This is two saponin levels of cosmetic ingredients that were provided. So I have gotten a little bit of information on what composition. And although the title does not say it of the table, I think that both panax ginseng -- I'd have to check for sure on what 14 is because just the trade name is listed in the title. But right here there's a big range in the saponin levels.

DR. LIEBLER: You're talking about Table 8, right?

DR. EISENMANN: Table 9.

DR. LIEBLER: Oh, Table 9.

DR. EISENMANN: Table 8 is also --

DR. LIEBLER: Table 8 and 9.

DR. EISENMANN: -- but Table 9 I think is published information referenced. It's published information so that's more likely to be a dietary supplement whereas this -- the information in Table 9 came from two cosmetic suppliers. It's hard to tell because you've got to go back and forth to the reference sections to see where things came from, whether it's on cosmetic ingredient or was published information. Table 9 is from cosmetic ingredient suppliers.

DR. BELSITO: Okay, so, safe as used. Discussion, pulegone not there because it's in the essential oil extract of a species that is not used.

MS. BECKER: Okay.

DR. BELSITO: So be it.

DR. BERGFELD: Are you going to leave it on the list?

DR. BELSITO: It's not on the list. It's the oil of the quinquefolius. Is it -- the oil of the quinquefolius is not listed as a cosmetic ingredient.

DR. BERGFELD: So, the panax ginseng root oil is different?

DR. BELSITO: Yes.

DR. BERGFELD: Okay. And you're not going to do anything with the read-across patchwork that you've discussed?

DR. BELSITO: I'm not sure what --

DR. BERGFELD: You're talking about you haven't got all the information on

the characterization of some of these.

DR. LIEBLER: Well, if you mean we're not going to do anything like delete those ingredients?

DR. BERGFELD: No, no, no. Just discuss them. Put a statement in.

DR. LIEBLER: I think, yeah, no, I think we have to have a statement. And the statement will be to the effect that detailed composition chemicals -- I can write something, obviously, but it will be something to the effect that a chemical composition was not available for all of these ingredients, was available for one of the ingredients. Two of the ingredients, I guess. The saponins and the ginseng root extract. Not available for the others. The panel -- the reason -- similar toxicity data for some of the others and low use concentrations to conclude that there wasn't a basis for viewing these differently. Something to that effect.

DR. BERGFELD: Thank you.

DR. SNYDER: Yeah, I think it's complicated because you have to have this chemical composition data and then you have to have the tox data to say that there's no red flags. And so the language is going to be difficult to craft that. But once you have that crafted, then you can relay in the discussion what inferences we made across to the other ingredient.

DR. BELSITO: Okay. Dan, you have some homework tonight to craft that language. Thank you.

MS. BECKER: Can I clarify something? We're saying pulegone is not in there because it's in the essential oil of the root and the oil is not an ingredient.

DR. BELSITO: It's in the essential oil. It was only reported to be in the essential oil of the quinquefolius and the essential oil of the quinquefolius is not listed as a cosmetic ingredient.

MS. BECKER: Right. Okay, that clears it up because I was wondering if it was -- if the root was an ingredient, which it is for panax ginseng, would we have to leave that in? Because it just means that, as far as I can tell, that the root is dried and ground up. Just clarifying for my thought process. But we're not using quinquefolius whole; we're using it just as an extract as far as we know.

DR. BELSITO: It would help if I had -- so the ingredients for quinquefolium are strictly the root extract.

MS. BECKER: And because this is an oil and not the extract, you're not going to worry about it.

DR. BELSITO: I would assume as we heard from the presentation earlier, I guess it depends upon what kind of extract it is. So --

MS. BECKER: Sorry, just wanted to clarify.

DR. BELSITO: -- maybe we do have to worry about it, that there could be the oil in the extract. It doesn't say aqueous extract, does it? It just says extract.

MS. BECKER: We can extract it with anything.

DR. EISENMANN: You can say your expecting is that it's not in there and that if it is, you should follow the limit of -- the similar limit as you've described for peppermint oil if you want to go that way.

DR. BELSITO: Well, I mean --

DR. EISENMANN: Based on the information you have, you're not expecting it to be in there.

DR. BELSITO: We have an NOAEL for pulegone of 20 mg/kg/day and, I mean, I think if we're going to be addressing it, we need to address it, again, in a sense for the potential level of that impurity in the entire finished product -- Halyna is shaking her head -- in the discussion at least.

DR. BRESLAWEC: I'm very comfortable addressing the discussion. And the

other thing I think is the lack of data supporting estrogenic effects that would need to be discussed.

DR. BELSITO: Yeah, that was where we started, that we're comfortable with the current language in the report, that it didn't need to be expanded.

So then in the discussion I guess we do need to mention something about pulegone. We do need to perhaps pull in that information from the peppermint report with the NOAEL. That it's our understanding that levels of pulegone would not likely exceed that based upon the concentrations that these are used in but, P.S., be aware of that, something to the effect that when used with other botanicals that might contain this form, they also need to be aware that NOAEL for pulegone that's been established. And all that should be put in the discussion.

MS. BECKER: Got it.

DR. BELSITO: And Dan will draft something for the discussion regarding why we used the whole group and the read- across for the composition.

Okay. Anything more on panax ginseng root? Okay.

Dr. Mark's Team

DR. MARKS: Green Book. We're with ginseng. So in November the Panel tabled a review of these 13 ingredients. We wanted information of phytoestrogenic activity. Then we also had the -- is it pulegone, how do you say that? -- question whether or not there should be a limit. So I guess we're to the point do we move on issue a tentative report. Is it safe, Tom? How do you like the pulegone less than or equal 1 percent, okay?

DR. SLAGA: I'd say safe as used.

DR. MARKS: Safe as used.

DR. SLAGA: It's extremely weak.

DR. SHANK: Yeah, I had safe as used, too.

DR. MARKS: As you remember the phytoestrogenic affect, Don Belsito really raised that issue. It's in the minutes on page 7.

DR. SLAGA: Yeah, that's related to that one case.

DR. MARKS: Yeah, one case. Okay. So --

DR. SLAGA: But we do have developmental defects related to this. That's where you were confident that it was probably just a mistake.

DR. MARKS: So safe?

DR. SLAGA: Safe.

DR. MARKS: So we would issue a draft tentative report with a conclusion safe. And that's what I will move tomorrow. Anything specific in the discussion? We're going to ignore that one cream. And then, Tom, did you -- in the discussion of pulegone, any concerns about that? Do we need any specifics in the discussion or we'll see what that comes out when Lillian does that.

DR. SLAGA: Okay.

MS. BECKER: Dr. Belsito brought up an interesting thought that we now have two ingredients where pulegone is a possible issue, and that he has seen products with multiple botanical ingredients on there. So he wanted added into the discussion additive pulegone. If you're going to put this, you can't go over a certain amount in your total additives.

DR. SLAGA: The total from any extract.

MS. BECKER: Right, for the total of the extracts. You've got four in there.

DR. HILL: So in other words, if this were combined with peppermint oil, for example, then that would --

MS. BECKER: Right.

DR. MARKS: So is that in the discussion?

DR. SHANK: Not now. We'll have to add that.

DR. MARKS: Well, no. Yeah, exactly.

DR. SLAGA: But put it in the discussion.

DR. MARKS: Doesn't need to go in the conclusion?

DR. SLAGA: No.

DR. MARKS: Because right now, if you look on page 31, the last sentence in the conclusion says "the concentration of pulegone in these ingredients should not exceed 1 percent." So should you -- do you want to keep it at that or do you want to move the whole pulegone up into the discussion and just talk about multiple ingredients? So it actually is in the discussion, or I mean in the conclusion.

DR. SLAGA: Do we want that level for all extracts combined?

DR. MARKS: Do we even include that in the conclusion?

DR. SHANK: We usually do -- well --

DR. MARKS: We do put limits on ingredients, but now we're in a --

DR. SHANK: An impurity.

DR. MARKS: An impurity, yes.

DR. ANDERSEN: Well, that's not unheard of. Acrylamide monomer in polyacrylamide we flag as something that should be limited. So there is some precedent for talking about it. There's also no reason that the statement as stands couldn't be footnoted to acknowledge that we don't care whether it's from this ingredient or multiple ingredients, in formulation pulegone should not -- in a sense -- actually, no I'm wrong because the way we phrased it is "the concentration of pulegone in these ingredients," and we've actually gone away from that. I mean who cares how much is in the ingredient. The only thing we care about is what's in the formulation. So this should be recast to target the formulation with an appropriate number. And if it's 1 percent in the ingredient, then you need to look at what's the maximum use of ginseng. And I think we can work out an in-formulation level. But that is the -- the Panel has transitioned from talking about limiting concentration in an ingredient to limiting concentration in the formulation. And I think all in all, I'm much more comfortable with that as an approach. This would have been an anachronism that I didn't pick up before.

DR. MARKS: So would you suggest, Alan, that that last sentence not be part of the conclusion, but be transferred into the discussion with a bit more robust --

DR. ANDERSEN: It'd be a lot easier to explain in the discussion.

DR. MARKS: Yes, okay. So we will take that last sentence and move that up into the -- as you see in the discussion, it already exists, the one, two, three, fourth paragraph starts with "pulegone." So it could be incorporated in that paragraph, Lillian.

MS. BECKER: Uh-hum.

DR. MARKS: Okay. And you're okay with that total -- that 1 percent? Anything that's percent or less with pulegone in the formulation, Tom, you're not concerned from a safety issue?

Okay. So tomorrow I'm going to move that a draft tentative report be issued with these ingredients are safe at the present use and concentration.

Day 2

DR. MARKS: In December, the expert panel tabled the draft report on the ginseng root derived ingredients. We feel now that we're in the position that we can move forward with a draft tentative report with a conclusion of safe for these root-derived ingredients.

DR. BELSITO: Second.

DR. BERGFELD: Is there any other discussion?

DR. BELSITO: First of all, I think Lillian did a very good job about handling

the issues of phytoestrogenic activity. We felt that didn't need to be further expanded. We also noted in the panax quinquefolius root where they have those very high levels of pulegone, it's from the root essential oil which is not a cosmetic ingredient so we felt that that was not an issue. Furthermore, we went back to the peppermint report which demonstrated that the NOAEL for pulegone was 20 milligrams per kilogram per day and in the way that these would be used it would be below that NOAEL even if there were components of the essential oil in the quinquefolius and we thought that that should go in the discussion.

DR. MARKS: Don, did your team feel when you look on Panel Book page 31 under the conclusion the last sentence there is the concentration of pulegone in these ingredients should not exceed 1 percent, we thought that that could be moved up into the discussion and did not have to be in the conclusion and obviously when we now have multiple botanicals that might have pulegone in them, it's the addition of all of those and not just the single ingredient.

DR. BELSITO: Right. As we discussed, the issue is when you say that pulegone should not be at 1 percent in this product, a different botanical may be used in a much higher or lower concentration resulting in a very different concentration of pulegone or thujone or quercitin or whatever we're concerned about in that, so we would agree with striking that from the conclusion and putting it into the discussion.

DR. BERGFELD: It's been moved and seconded that we move forward with a safe conclusion for the ginseng group. Is there any other discussion? Seeing none, I'll call for the vote. All those in favor please indicate by raising your hand. Thank you. Unanimous.

Report

Safety Assessment of Panax spp. Root-Derived Ingredients as Used in Cosmetics

Status: Draft Final Report for CIR Expert Panel Review
Release Date: August 17, 2012
Panel Meeting Date: September 10-11, 2012

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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ABSTRACT

The Cosmetic Ingredient Review Expert Panel (the Panel) reviewed the safety of 13 Panax spp. root-derived ingredients as used in cosmetics. Panax spp. is used to designate the multiple species being considered. Panax "spp." is a short way of saying that multiple species within the genus are used in cosmetics, but not all species within that genus. These ingredients function mostly as skin-conditioning agents-miscellaneous, fragrance ingredients, skin conditioning agents-humectant, skin-conditioning agents-emollient, and cosmetic astringents. The Panel reviewed available animal and human data related to these ingredients. The Panel found that there was little to no possibility of phytoestrogenic activity caused by any of these ingredients. The Panel concluded that these Panax spp. root-derived ingredients are safe in the practices of use and concentration as presented in this safety assessment except that the Panel limited the amount of pulegone in these ingredients or in combination with other ingredient in a cosmetic product to < 0.03% in rinse-off products and 0.002% in leave-on products.

INTRODUCTION

Panax ginseng C. A. Meyer of the Araliaceae family is also called Chinese ginseng, Manchurian ginseng, or Korean ginseng.[1] It is a perennial herb indigenous to the mountainous forests of North China, Manchuria, and Korea. There are four other closely related plants of the Araliaceae family: *Panax quinquefolium* L. (American ginseng), *Panax japonicus* C. A. Meyer (chikusetsu ninjin or Japanese ginseng), and *Panax pseudoginseng* Wall (notoginseng, San-ch'i ginseng, and Himalayan ginseng). For the sake of brevity, Panax spp. is used to designate the multiple species being considered. Panax "spp." is a short way of saying that multiple species within the genus are used in cosmetics, but not all species within that genus.

Several ginseng-derived materials are used in cosmetics. The majority of uses in cosmetics involve root-derived ingredients, as distinct from ingredients derived from other plant parts. This safety assessment focuses on those ginseng ingredients that are derived from the root portion of the plant, and does not address ginseng-derived ingredients that are prepared using other plant parts. The ingredients included in this review are:

- panax ginseng root extract,
- hydrolyzed ginseng root,
- hydrolyzed ginseng root extract,
- hydrolyzed ginseng saponins,
- panax ginseng root,
- panax ginseng root powder,
- panax ginseng root water,
- panax ginseng root oil,
- panax ginseng root protoplast,
- panax japonicus root extract,
- panax notoginseng root,
- panax notoginseng root powder, and
- panax quinquefolium root extract.

The cosmetic functions of these ingredients include: skin-conditioning agents-miscellaneous, fragrance ingredients, skin conditioning agents-humectant, skin-conditioning agents-emollient, and cosmetic astringents.

There is some confusion as to whether or not *P. ginseng*, *P. quinquefolius*, *P. japonicus*, and *P. pseudoginseng* are used in cosmetics under their own names, all as *P. ginseng*, or interchangeably under the generic name "ginseng". There is also speculation that there is no real difference among these plants in cosmetic application.[2] Because this is unresolved, each of these ingredients will be referred to specifically in this safety assessment.

To address the difficulty in assessing the properties and biological effects of ginseng, standardized extracts of both *P. ginseng* C.A. Myer (G115) and *P. quinquefolium* (CNT-2000) have been developed.[3] These extracts are standardized by the content of 6 saponins (Rb1, Re, Rc, Rd, Br2, and Rg1) and are used in several of the studies in this report. However, the composition of G115 and CNT-2000 is proprietary information and is not available.[4]

CHEMISTRY

Definitions

The names, CAS Registry Nos., functions, and definitions of the ingredients in this safety assessment are listed in Table 1. CAS No. 50647-08-0 is generically used for several of the ginseng root ingredients, but several ingredients have no CAS Nos.

The *International Cosmetic Ingredient Dictionary and Handbook* defines the terms extract, powder, oil, and water included in the names of these ingredients.[5]

Extract – Extracts are identified by the source of the material extracted. The INCI names for extracts represent the material that is extracted from. Many extracts are supplied with the extracting solvent and/or other diluents. Where evidence of isolation is presented, a botanical ingredient may be named as a chemical entity.

The INCI names for plant extracts prepared by solvent extraction are assigned labeling names that identify the name of the plant and the solvent. When the extraction solvent is carbon dioxide, carbon dioxide is not included in the INCI name since it evaporates. Additionally, solvents are not identified in the INCI name in cases where the solvent has been driven off and is not present in the final preparation.

Powder - The term "powder" is applied to the names for botanical materials that have been mechanically ground, irrespective of particle size.

Oil - The term may be used to name non-triglycerides when it applies to ingredients that are commonly recognized (e.g., panax ginseng root oil). Essential oils are prepared by a steam distillation process that yields two distinct fractions, a water-insoluble fraction and a water-soluble fraction. The water-insoluble fraction contains the term oil in the name, e.g., panax ginseng root oil.

Water - The term refers to the water soluble fraction from the steam distilled plant material and is identified by the term 'Water" in the INCI name. The term water that refers to the instance wherein the water has come in contact with the named material does not apply here as it is different from an ingredient that is prepared by adding water to a material prepared by solvent extraction; the ingredient would then be called a mixture, e.g., water (and) juniperus communis fruit extract.

Method of Manufacture

In general, ginseng or ginseng root refers to the dried root of the *P. ginseng, P. quinquefolius*, *P. japonicus*, and *P. pseudoginseng* plants. The plants may be from wild or cultivated sources.[6] If the root is raw or dried, then it is referred to as "white" ginseng. If it has been steamed and dried before extraction or pulverizing, it is referred to as "red" ginseng because of a change in coloring.[7] If it is steamed and dried 9 times, the coloring darkens more and the product is referred to as "black ginseng".[8,9]

ROOT EXTRACT - The extraction is performed by percolation with aqueous alcohol solution (60%) and then concentration under vacuum to dryness or percolation with propylene glycol followed by concentration under vacuum.[10] The solvent for the root extract may be propylene glycol, propylene glycol + water, propylene glycol dicaprylate/dicaprate, butylene glycol, ethanol, ethanol + water, glycerin + water, caprylic/capric triglyceride, or helianthus annuus (sunflower) seed oil.[11] One supplier reports "aging" the panax ginseng root in ethanol and butylene glycol (70% aqueous) for 6 weeks before filtering and evaporating the ethanol. This procedure results in a total of 4.61 ± 0.98 mg/g dry weight ginsenosides (2.75 ± 0.7 triol, 1.86 ± 0.3 diol, 0.73 ± 0.11 mg/g diol/triol).

One manufacturer reported the extraction process grinds the whole dried red ginseng and places the ground ginseng root into an extraction solvent of ethanol (70%) for 12 h at 20 -25°C.[12] The solvent is then filtered and evaporated to remove the ethanol to < 1%. The product is then centrifuged, dried, and sterilized.

SAPONINS - Saponin glycosides are extractable from the ginseng roots with hot water or alcohols.[1]

Saponins may be extracted from fresh raw *P. quinquefolium* root using methanol (30% - 100%) at room temperature, over heat, or under microwave conditions. Each of these processes gives a different ratio of saponins (i.e., Re, Fb1, mRb1) in the extract.[13] Variation in yield and type of yield also depends on sample size, extraction time, sample to solvent ratio, and solvent concentration.

One manufacturer reported the use of ultrahypothermia biotic extraction techniques to selectively yield ginsenosides.[14] However, there is no further explanation about this process.

Temperature influences the extraction kinetics, solvent viscosities, extraction efficiencies, and overall recoveries in ultrahigh-pressure extraction.[15] Using 70% aqueous ethanol at 200 MPa, 60ºC was optimal for saponin yields. Other temperatures led to a decreased yield of saponin compounds.

Analytical Methods

Powdered ginseng may be verified by running it on thin-layer chromatography and comparing with a standard preparation under UV light.[8]

Impurities

Analysis of a panax ginseng root extract concentrate showed lead, cadmium, and mercury were below the detection limits of < 0.040, 0.051, and < 0.010 mg/kg, respectively.[16] Aflatoxin B1 was measured at < 0.3 µg/kg and B2, G1, and G2 at < 0.3 µg/kg. Analysis of multiple pesticides showed that most of them were not detected except for DDE (0.02 mg/kg), total DDT (0.03 mg/kg), total HCH (0.030 mg/kg), Quintozen (0.020 mg/kg), and Pentachloranilin (0.020 mg/kg). Results of a microbiologic analysis, aerobic bacteria was found at 45000 CFU/g, fungus at 20 CFU/g, and Escherichia coli at <10 CFU/g.

A panax quinquefolium root extract was reported to have 20 ppm of heavy metals and 2 pm of arsenic.[12]

Ginseng root extract product mixtures may contain low concentrations of preservatives such as 0.5%-0.7% Bactiphen 2506 G (phenoxyethanol, methylparaben, ethylparaben, propylparaben, butylparaben).[11]

None of 35 fragrance allergens identified by the European Union were detected in panax ginseng root extract.[14]

Physical and Chemical Properties

The available physical and chemical properties of ginseng root-derived cosmetic ingredients are provided in Tables 2 and 3.

Panax quinquefolium root extract is stable for 2 years in a sealed container.[12] This extract was stable at 1%, 2%, and

3% in ethanol at pH 2-10 (time not specified) and at 1%, 3%, and 5% at 40 - 80°C for up to 120 min.

Saponins form colloidal solutions in water which foam upon shaking (frothing) and have a bitter taste.[1]

Constituents

According to the *Handbook of Phytochemical Constituents of GRAS Herbs and Other Economic Plants* and Dr. Duke's Phytochemical and Ethnobotanical Databases, the constituents of ginseng roots include: saponins and sapogenins, carbohydrates, organic acids (including amino acids), non-protein nitrogenous substances, peptides, minerals, and enzymes.[2,17-20] The known constituents of *P. ginseng, P. quinquefolius*, *P. japonicus*, and *P. pseudoginseng* roots, and their concentration in the plant root, are listed in Tables 4 - 7.

In Table 5, pulegone was reported as a constituent of *P. quinquefolius*. Because of the toxicity of pulegone, in an earlier safety assessment of peppermint oil, the safety of the ingredient was assured only when the levels of pulegone were limited to ≤ 1% in the ingredient.[21]

Saponins (or ginsengosides), a sweet-bitter material, usually exist in plants in the form of glycosides known as "saponin glycosides".[1] Saponin glycosides are macromolecules and are composed of a "sugar" (glycone) and a "non-sugar" (aglycone). The aglycone is also called genin. The aglycones of ginseng are called sapogenins. The chemical structures of some of the prominent saponins in ginseng are shown in Figure 1.

More than 40 different saponins have been identified and isolated from the root of *P. ginseng*.[22] Each saponin has at least 2 (carbon-3 and -20) or 3 (carbon-3, -6 and -20) hydroxyl groups, which are free or bound to monomeric, dimeric, or trimeric sugars. Saponins also exist as stereoisomers having either of two configurations for the position of hydroxyl group on carbon-20. Based on their chemical structures, saponins are generally divided into 2 groups: protopanaxadiols (PPD) and protopanaxatriols (PT). The sugar moities in the PPD group attach to the 3-position of a dammarane-type triterpine as in Rb1, Rb2, Rc, Rd, Rg3, Rh2, and Rh3 (Fig. 1A), whereas the sugar moities in the PT group attach to 6-position of dammarane-type triterpine as in Re, Rf, Rg1, Rg2, and Rh1 (Fig. 1B). The pseudoginsenoside F11 belongs to PT group, although the alkyl chain at the 20-position is replaced by a tetrahydrofuran ring (Fig. 1D).

Analysis of commercially available panax ginseng root preparations (both powder and liquid) show that these vary widely in the amount of saponins (Rb1, Rb2, Rc, Rd, Re, Rf, and Rg1).[23] Panax ginseng root extract is reported to have a ginsenoside content of 0.2-0.3%.[11] The saponins Rg1, Re, Rb1, Rc, Rb2, and Rd make up > 90% of the saponin content of *P. ginseng* root.[24] Fresh roots have yielded higher amounts of panaxatriol (Re +Rf + Rg1 + Rg2 + Rh1; 2.8 mg/g DW) and panaxadiol (Rb1 + Rb2 + Rb3 +Rc +Rd + Rg3; 16 mg/g DW) saponins compared to dried roots and powdered roots.[25]

There are several chemical composition differences between *P. ginseng* and *P quinquefolium* root. Rf is present in *P. ginseng* but not *P. quinquefolium*. The opposite is true for pseudoginsenoside F11.[26] Steaming the roots causes chemical degradation and conversion of original saponins to new compounds. Steaming is also associated with a decrease in the polar saponins Rg1, Re, Rb1, Rc, Rb2, Rb3, and Rd and an increase in the less polar Rg2, Rg3, Rg5, Rh2, Rk1, and Rs4.[27-29]

Table 8 shows the content of some of the saponins in both white (dried, unsteamed) and black (the steaming and drying process repeated 9 times) *P. ginseng*. The polyphenol content is greater in black ginseng (~ 35 mg/g) than in white ginseng (~ 20 mg/g).[9] Table 9 shows a comparison of saponin content by extraction technique.[11,14]

OTHER GINSENG CONSTITUENTS

Carbohydrates were reported to be obtained in the aqueous extract of ginseng root in small amounts, and were present as many different types of sugars or polysaccharides.[30-33] The most common monosaccharides from ginseng sources were glucose and fructose. Maltose and sucrose were the most common disaccharides. Trisaccharides, tetrasaccharides, and oligosaccharides are also found in ginseng root, as well as ginseng pectin, a crude polysaccharide.

Non-amino organic acids are present in alcohol extracts of ginseng roots. The most common organic acids are citric, fumaric, ketoglutaric, maleic, malic, pyruvic, succinic, and tartaric acids and the fatty acids oleic, linoleic, and linolenic acids.[34,35]

The free amino acids found in ginseng are arginine, histidine, lysine, leucine, theonine, valine, phenylalanine, alanine, asparatic acid, glutamic acid, glycine, proline, tyrosine, and serine.[36] The amount of free amino acids in raw *P. ginseng* roots decreases when the roots are steamed, more so at 120ºC than 100ºC.[37]

Another nitrogenous substance in ginseng root is choline.[38]

Constituents reported for specific ingredients are:

PANAX GINSENG ROOT

To comply with the Japanese Phannacopeia, the dried material of both raw and steamed roots, Panax ginseng root must contain > 0.10% gensenoside Rg1 and > 0.20% ginsenoside Rb1.[8]

PANAX GINSENG ROOT POWDER

To comply with the Japanese Phannacopeia, the dried material of Panax ginseng root powder must contain > 0.10% gensenoside Rg1 and > 0.20% ginsendoside Rb1.[8]

The percentage of ginseng saponins from one sample of freeze-dried red ginseng extract powder was ~ 3.3%.[39] Ginseng saponins present were Rb1 (15.8%), Rb2 (7.8%), Rc (8.1%), Rd (7.6%), Re (3.2%), Rf (4.7%), Rg1 (1.9%), Rg2 (22.2%), Rg3 (24.2%), Rh1 (4.7%) along with other minor saponins.

The concentration of saponins in ginseng root ingredients varies with the form. Ranges for food additives were

found to be 4% - 8% saponins (calculated as Rg1); actual root samples vary in their total saponin content from 0.5% - 3% (dry weight).[40,41]

PANAX GINSENG ROOT OIL

Ginseng oil contains volatile and non-volatile fractions. The low boiling fraction (boils from 71 to 110°C) contains the sesquiterpenes panacene and β-elemene (Figure 2). Panacene gives the characteristic fragrance of ginseng. The high boiling fraction (boils from l20 to 150°C) contains panaxynol.[42,43]

P. japonicus root oil yields were reported to be 0.451%, suggesting that one would need 15 pounds of root to produce 1 ounce of oil.[44]

USE

Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) and a survey conducted by the Personal Care Products Council (Council) collected use concentrations for ingredients in this group (Table 10).[45,46]

The total number of uses of panax ginseng root extract was 277 (196 leave-on products, 77 rinse-off products, and 4 diluted products) at maximum concentrations of 0.000002% – 0.5% (maximum of 0.5% in leave-on products, 0.3% in rinse off products, and 0.0004% in diluted products). This included a maximum of 0.1% in eye, nail, and shaving products and lipsticks; 0.01% in face powders; and 0.3% in hair products. The Council further reported that white panax ginseng root extract is used up to 0.04% in leave-on, 0.0003% in rinse-off, and 0.00009% in diluted products. Red panax ginseng root extract was reported to be used up to 0.003% in both leave-on and rinse-off products.

Panax quinquefolium root extract was reported to be used in 430 cosmetic products (286 leave-on, 140 rinse-off, and 4 diluted for bath products) at maximum concentrations of 0.002% in rinse-off products (no concentrations of use were reported for leave-on and diluted products) including 30 eye products, 114 hair products, and 5 lipsticks. Panax quinquefolium is used in 4 fragrance preparations and 5 hair sprays.

Panax ginseng root was reported to be used in 22 cosmetic products (16 leave-on and 6 rinse-off products; 2 underarm deodorants and 17 dermal contact products); there were no use concentrations reported for this ingredient. Panax notoginseng root was reported to be used at 0.0004% in dentrifrices; there were no uses reported to the FDA for this ingredient.

Panax ginseng root powder was reported to be used in one mud pack; no concentration of use was reported.

There were no uses reported for panax ginseng root powder, hydrolyzed ginseng root, hydrolyzed ginseng root extract, hydrolyzed ginseng saponins, panax ginseng water, panax ginseng root oil, panax ginseng root protoplasts, panax japanicus root extract, or panax notoginseng root powder.

Panax ginseng root extract, panax ginseng root, and panax quinquefolim root extract are used in fragrance preparation, hair sprays and/or deorderants up to 0.1% and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm compared with pump sprays.[47-50] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[49,51] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[52] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

Non-Cosmetic

Ginseng root is widely used as an herbal medicine for its alleged tonic effect and possible curative and restorative effects.[53-65] Modern therapeutic claims suggest that ginseng has beneficial effects on cognitive function, physical and psychomotor performance, immune-modulation, diabetes mellitus, and herpes simplex type-II infections.[56,60,61,65-68] However, a systematic review of randomized controlled trials found that the efficacy of ginseng root extract could not be established for any of these effects.[69]

When used as a dietary supplement, unless otherwise prescribed, the recommended daily dose (taken in the morning) is dried root 0.5–2 g by decoction; doses of other preparations would be calculated accordingly.[70] Ginseng is often an ingredient in energy drinks.

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

In some experiments studying the effects of ginseng, the metabolite of the saponin Rb1, "Compound K" (20-*O*-B -D-glucopyranosyl-20(S)-protopanaxadiol), is used. Rb1 is poorly absorbed from the gut. Compound K is produced from Rb1 by a stepwise degradation of sugar moieties by intestinal microflora.[71-73]

Dermal/Percutaneous/Inhalation

No data were discovered on the dermal/percutaneous or inhalation absorption of ginseng root-derived ingredients.

Oral/Intravenous/Intraperitoneal

PANAX GINSENG ROOT

Panax ginseng root (1 to 2 g in capsules; G115) was orally administered to subjects (n = 2) on empty stomachs.[74] Blood and urine were sampled before and periodically for up to 24 h after administration and were analyzed for saponins. In the plasma, at ~0.75-3.25 h, Rh_1 was detected; ~3.75-5.25 h, hydrated Rh_1; ~5.25-8.25 h, Rb1; ~7.5-10.75 h, compound K; ~8-11.75 h, f_1/Rh_1 (not distinguished between the two); ~8.75-10.25 h, hydrated compound K. In the urine at 0-3 h, Rg1, Rd, Re, Rb2, and Rc were detected. At 3-6 h, Rh_1 was detected; 6-12 h, Rb1 and compound k; and at 12-24 h, f1/Rh1 and compound k were detected.

GINSENG SAPONINS

The absolute bioavailability of Panax saponins were reported to range from 0.26% - 64.8% (Table 11).

The low bioavailability of saponins may be attributable to their breakdown in the gastrointestinal tract, metabolism by intestinal microflora and excretion in bile or urine.[75] It is also suggested that low membrane permeability may be an important factor in determining the extent of absorption.

The absolute bioavailability of the saponin 25-OH- protopanaxadiol is 64.8±14.3% (range 44.1–75.9%) which is the highest among the reports on ginseng compounds.[76] The higher absolute bioavailability is found in the rats and the author suggests that this can be explained by the deglycosylated mother aglycone structure, lower molecular weight, and higher hydrophobility of 25-OH-PPD compared to saponin Rg3.

The National Toxicology Program reported that the degradation and metabolism of saponins has been studied in animals and *in vitro* using acids, enzymes, and intestinal bacteria.[72,77-80] After oral administration, the protopanaxatriol saponins are hydrolyzed to saponin Rh1 and is hydrated form under acidic conditions similar to gastric fluid. Protopanaxadiol saponins (Rb1) are metabolized to M1 [20-*O*-B -D-glucopyranosyl-20(S)-protopanaxadiol] or compound-K in rats and humans by intestinal anaerobes via stepwise cleavage of the sugar moieties.[78] Strains of the intestinal bacteria *Prevotella oris* hydrolyze Rb1.[81] Protopanaxadiol is formed from Rh2 as a result of deglycosylation by B16 melanoma cells in vitro.[82]

The absorption of Rb1 from the intestine of rats was low.[72] In mice, after an oral dose of Rb1 or M1 (2 mg/mouse), the M1 level in the serum gradually increased, peaked at 8 hours after oral administration of Rb1, and decreased with time; intact Rb1 was not detected in the serum.[83] The level of M1 in the serum reached maximum at 8 h (8.5 +/- 0.4 μg/ml) after Rb1 administration and at 2 h (10.3 +/- 1.0 μg/ml) after M1 administration.

Rg1 was rapidly absorbed (30% after 1 hour) and metabolized by mice after oral administration. Mouse urine and feces contained little unchanged Rg1 but did contain high levels of metabolites including Rh1 and saponin Rg1 (protopanaxatriol). Rg1 showed an extremely short half-life of 27 min after intravenous administration to mini-pigs. In contrast, the protopanaxadiol saponin Rb1 showed a half-life in the β-phase of 16 hours.[84]

In several experiments using male New Zealand White rabbits, saponins (A1, Rg1, Rd, Re, Rb2) were administered by oral, intraperitoneal (ip), and intravenous (iv) routes (Table 12).[85] In the oral experiment, no saponins were observed in the plasma, urine, or feces. The authors suggested that this is due to poor absoption in the gastro-intestinal tract, binding within the gastro-intestinal tract, microorganism metabolism, or an unreliable animal model.

In humans, saponins are present in urine after oral ingestion.[86,87] About 1.2% of the dose was recovered in 5 days. Generally, saponins are very poorly absorbed following oral administration in vivo.

Cytotoxicity

PANAX GINSENG ROOT EXTRACT

In an in vitro assay, panax ginseng root extract (0, 100, 250, 500, 1000 μg/ml in ethanol) was not cytotoxic to human dermal fibroblast cells.[88]

TOXICOLOGICAL STUDIES

Acute Toxicity

Non-Human

PANAX GINSENG ROOT EXTRACT

The LD_{50} values using rodents for the root itself and for various forms and fractions of panax ginseng root extract administered orally and ip are listed in Table 13.

Repeated Dose Toxicity

Dermal

PANAX GINSENG ROOT EXTRACT

In a therapeutic efficacy test of red panax ginseng root extract concentrate (0.2 ml) and Rg2 (1%; 0.2 ml), the test

material was applied to the backs of 5-week-old female C57BL/6 mice after "shav[ing] with hair removal tape" for 14 days. No adverse effects were observed during treatment.[12]

Oral - Non-Human

PANAX GINSENG ROOT EXTRACT AND PANAX QUINQUEFOLIUS ROOT EXTRACT

Male Wistar rats (n = 5) were orally administered *P. ginseng* root water extract, heat-treated *P. ginseng* root water extract, *P. quinquefolius* root water extract, or heat-treated *P. quinquefolius* root water extract (0, 100 mg/kg/d) by gavage for 15 days.[89] The extracts were heat treated by autoclave at 120ºC for 3 h then placed in an oven at 50ºC for 3 days. Blood and urine were collected. No clinical signs or decreases in renal or hepatic function parameters of the treated rats were observed.Panax ginseng root extract in the form of G115 (0, 1.5, 5, or 15 mg/kg/day) was administered in the feed of Beagle dogs (n = 4/sex) for 90 days.[90] No consistent, dose-response relationship occurred and all values (weight gain, hematology, urine chemistry) were within normal physiological ranges for Beagle dogs. Gross and microscopic examinations of major organs revealed no morphological or pathological effects. No evidence of toxicity was observed. The highest dose, 15 mg/kg, is approximately twice the recommended dose for humans.

LACa mice (n = 90) were administered panax ginseng root extract (aqueous extract; 8 mg/kg/d; 40 mg of whole root) in drinking water 1) from 8 weeks of age throughout life, 2) from 52 weeks throughout life, and 3) none.[91] There were no differences in mean weights or survival observed in the mice. Increased behavioral responses to mild stress were observed in the treatment groups.

It was reported in a review that rats (n and strain not provided) were orally administered panax ginseng root extract (105-210 mg/kg/d) for 25 weeks.[92] No toxic effects were observed. No further details on this study were provided.

P. ginseng root extract extracted with 80% aqueous ethanol was used in the next four studies.

F344/N rats (n = 5/sex) were administered; 0, 125, 250, 500, 1000, or 2000 mg/kg in 0.5% aqueous methylcellulose) by gavage 5 days/week for 16 days.[93] All rats survived to the end of the study. Mean body weight gain of 2000 mg/kg males was greater than that of the vehicle controls. There were no chemical-related gross or microscopic findings attributed to the administration of ginseng.

B6C3F1 mice (n = 5/sex) were administered *P. ginseng* root extract (0, 125, 250, 500, 1000, or 2000 mg/kg in 0.5% aqueous methylcellulose) by gavage 5 days per week for 17 days.[93] All mice survived to the end of the study. The final mean body weight of 1,000 mg/kg males was significantly less than that of the vehicle controls; all other groups were similar to controls. There were no statistically significant chemical-related gross or histopathologic changes in dosed mice.

F344/N rats (n = 10/sex) were administered panax ginseng root extract (0, 1000, ,000, 3000, 4000, or 5000 mg/kg) in sterile water by gavage 5 days/week for 14 weeks.[93] All rats survived to the end of the study. Mean body weights of all dosed groups were similar to those of the vehicle control groups. No lesions that were observed by gross or histopathologic examination were attributed to the administration of panax ginseng root extract.

B6C3F1 mice (n = 10/sex) mice were orally administered panax ginseng root extract (0, 1000, 2000, 3000, 4000, or 5000 mg/kg) 5 days per week for 14 weeks.[93] All mice survived to the end of the study. Mean body weights of all dosed groups were similar to those of the vehicle control groups. Although sporadic incidences of lesions were observed in the vehicle control and 5,000 mg/kg groups, there were no chemical-related gross or microscopic findings in dosed mice.

Inhalation – Non-Human

No data was discovered on the repeated dose inhalation toxicity of ginseng root-derived ingredients. However, a material safety data sheet stated that panax quinquefolium root extract may be irritating or toxic if inhaled.[12]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

PANAX GINSENG ROOT EXTRACT

There were no adverse effects reported in two oral reproductive/developmental studies of panax ginseng root extract up to 20 mg/kg using rats (Table 14).

Subcutaneous administration of a ginseng extract (extracted with ethanol; 0.5 ml/g) for 5 days enhanced the mating behavior of male rats.[94] The extract further stimulated spermatogenesis in rat and rabbit testes, and increased the motility and survival of rabbit sperm outside the body.[95]

SAPONINS

In screening tests with whole immersion of embryos, the saponins Rb_1 (30-50 μg/ml) and Re (50 μg/ml) yielded changes in morphological scores in rat and mice embryos (Table 15). Rc (5, 50 μg/ml) had no effect on the morphological scores of rat embryos.

Saponins (6 mg/2 ml injection; composition not provided) injected into male rats (n = 10; strain not provided) for 7 consecutive days did not increase testosterone levels in the plasma.[96]

GENOTOXICITY

PANAX GINSENG ROOT EXTRACT

Panax ginseng root extract (0-1 mg/ml) produced inhibitory effects on DNA synthesis/mutagenesis, measured by thymidine incorporation into V79 Chinese hamster lung cells.[97]

GINSENG SAPONINS

In an assay of the effects of saponins on mitosis, Rg1 stimulated mitosis in the bulb and seedling root tip cells of *Allium cepa* . It was most effective at 0.002 - 0.006 mg/ml. In contrast, saponin Rb1 (0 - 0.01 mg/ml) inhibited mitosis in the same cell line in a dose dependent manner.[98]

An aqueous and a 1-butanol extract containing saponins from P. quinquefolius roots (up to 36 mg/ml) was not mutagenic in Salmonella typhimurium (TM677) with or without metabolic activation.[99]

PANAX GINSENG ROOT POWDER

Dried Panax ginseng root powder dissolved in water (100 mg/ml) was negative in genotoxicity tests using *Bacillus subtilis* strains H17Rec+ and M45Rec- and in *S. typhimurium* (TA98, TA100) with or without PCB-induced rat liver S9.[100]

PANAX GINSENG QUINQUEFOLIUS

A water extract of *P. quinquefolius* roots (up to 36 mg/ml) was not mutagenic in *Salmonella typhimurium* (TM677) with or without metabolic activation.[99]

An Ames test of panax ginseng quinquefolius (extracted with water/butylene glycol; 30% - 70%) using *S. typhimurium* (strains TA98, TA100) did not demonstrate a potential for mutagenicity.[12]

CARCINOGENICITY

PANAX GINSENG ROOT EXTRACT

Panax ginseng root extract (solvent not provided; 0, 50, 75 ppm in feed) did not increase the number of aberrant crypt foci in rat colons (n = 10).[101]

F344/N rats (n = 50/sex) were administered panax ginseng root extract (0, 1250, 2500, or 5000 mg/kg) in sterile water by gavage for 5 days/week for 104-105 weeks.[93] Survival of 5000 mg/kg females was statistically significantly less than that of the vehicle controls; however, the deaths were not attributed to the administration of ginseng. Mean body weights of high dose females were less than those of the vehicle controls after week 61 of the study, and mean body weights of other dosed groups of rats were similar to those of the vehicle controls throughout the study. No increases in the incidences of neoplasms or nonneoplastic lesions were attributed to the administration of ginseng. The incidence of mammary gland fibroadenoma was statistically significantly decreased in the high dose females. There was no evidence of carcinogenicity under these conditions.

B6C3F1 mice (n = 50/sex) mice were administered panax ginseng root extract (0, 1250, 2500, or 5000 mg/kg) 5 days/week for 105 weeks.[93] Survival of dosed groups was similar to that of the vehicle control groups. Mean body weights of dosed mice were similar to those of the vehicle controls. No neoplasms or non-neoplastic lesions were attributed to the administration of ginseng. The incidence of mammary gland fibroadenoma was significantly decreased in the high dose female group. There was no evidence of carcinogenicity under these conditions.

Cancer Prevention

PANAX GINSENG ROOT

A number of in vitro and in vivo studies indicate that ginseng root and its extracts or its purified constituents have antitumor properties.[56,64,102-104] For example, the topical application of either the methanol extract of heat-processed *P. ginseng* or the purified saponin Rg3 to the shaved backs of female ICR mice suppressed 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced skin tumor promotion.[102] *P. ginseng* appears to inhibit tumor development, especially tumor promotion and progression, through anti-inflammatory, antioxidant, and apoptotic mechanisms involving changes in gene expression.[62,103,105-107] Other pertinent mechanisms under investigation involve the potential for ginseng and its constituents to influence immuno-surveillance and neurotransmission.[103] However, the evidence for the antitumor effects of ginseng in humans is not conclusive, and no clinical trials have confirmed the efficacy of ginseng treatments in cancer patients.

IRRITATION AND SENSITIZATION

Irritation

Dermal-Nonhuman

GINSENG SAPONINS AND OTHER CONSTITUENTS

Saponin Rb1 (0.05%) or the metabolite compound K (0.2, 0.05%) was administered to the ears of ICR mice (n = not provided) after sensitization to oxazolone.[108] Then a total of 20 µl of 1% oxazolone in a mixture of acetone and olive oil (4:1) was applied to both sides of the mouse ear every 3 days starting 7 days after sensitization. Ear thickness was measured. Seventy-two h after each application of the oxazolone, Rb1 was topically applied in a total volume of 20 µl to both sides of the ear 30 min before and 3 h after each application of oxazolone. There were no irritation effects reported for Rb1 or

compound K.

The above experiment was repeated with saponin Re (0.01%, 0.05%) and its metabolite Rh1 (0.01%, 0.05%) on 12-*O*-tetradecanoylphorbol- and oxazolone-induced dermatitis.[109] There were no irritation effects reported for either compound.

The above experiment was repeated with saponin Rg5 (0.05%) and its metabolite Rh3 (0.02%, 0.05%) on oxazolone-induced dermatitis.[26] There were no irritation effects reported for either compound.

Inclusion of panax ginseng root extract constituents Rh2 (0.1%) and Rh3 (0.1%) in a dermal test of TNCB reduced the appearance of severe erythema/hemorrhage, edema, excoriation/erosion and scaling/dryness compared to TCNB in verhicle alone using female NC/Nga mice (n = 7).[110]

In an ear thickness test, panax ginseng root extract saponins Rg3(0.02%, 0.05%), Rf (0.02%, 0.05%), and Rh2 (0.05%) applied to oxazolone-induced dermatitis on female ICR mice did not cause irritation and reduced the effects of the oxazolone.[111]

Dermal-Human

PANAX GINSENG ROOT EXTRACT

In a human patch test (n = 30) of panax ginseng root extract (extracted with dichloromethane, then ethanol, dry residue added to water; 0, 1, 10, 20, 100 mg/ml in petrolatum), the patch was left in place for 48 h. There were no reactions observed at 1 and 24 h after removal.[88]

In a human patch test (n = 30) of panax ginseng root extract (concentration not provided), the patch was left in place for 48 h. There were no reactions observed at 30 min and 24 and 48 h after removal.[14]

In a human therapeutic efficacy test (n = 15) of panax ginseng root extract (extracted with butylene glycol; concentration not provided), there were no adverse effects reported at the time of treatment and at 4 and 8 weeks.[14]

GINSENG SAPONINS AND OTHER CONSTITUENTS

Falcarinol (0.5 mg in ethanol) strongly aggravated histamine-induced edema, but did not induce edema by itself, in skin prick tests (n = 4).[112] The test was repeated on 2 of the subjects 1 week later with the same results.

Sensitization

PANAX GINSENG ROOT EXTRACT

A human repeated insult patch test (HRIPT; n = 99) of a cuticle serum containing Panax ginseng root extract (0.1%; 0.2 g) resulted in no dermal irritation or allergic contact sensitization.[113]

In a HRIPT (n = 219) of a lipstick containing Panax ginseng root extract (1%; 0.2 g), there were no adverse effects or signs of sensitivity.[114]

In a HRIPT (n = 104) of a night cream product containing panax ginseng root extract (0.1%; 0.2 g), there was no skin reactivity observed at any point in the study.[115]

PANAX QUINQUEFOLIUM

In a HRIPT (n = 10) of panax quinquefolium root extract (10% aqueous), there were no signs of irritation or sensitization observed.[12]

Sensitization Reduction

PANAX GINSENG ROOT EXTRACT

In a dermal test of 2-chloro-1,3,5-trinitrobenzene (TNCB) using female NC/Nga mice (n = 7), inclusion of panax ginseng root extract (red; 0.1%) reduced the appearance of severe erythema/hemorrhage, edema, excoriation/erosion and scaling/dryness compared to TCNB in the vehicle alone. [110]

In an ear thickness test, panax ginseng root extract (water extract of red ginseng; 0.02%) applied to oxazolone-induced dermatitis on female ICR mice did not cause irritation and reduced the irritation effects of the oxazolone.[111]

Phototoxicity

PANAX GINSENG ROOT EXTRACT

An ethanol extract of *P. ginseng* (100%; 30 µl) was not phototoxic to *Candida albicans* exposed to 50 J/cm^2 UVA radiation. Using the same treatment, hemolysis was observed in red blood cells.[116]

HaCaT cell were treated with ginseng root extract (0 or 1%) for 24 h and then exposed to UVB radiation (time not provided). At 24 h after UVB irradiation, survival was increased in the treatment group compared to controls.[14]

Panax ginseng root extract (100%; 10 pg/, 100 ng/mouse) or 3% vitamin C (1.5 mg/mouse) were applied topically to the dorsal region of each male albino hairless HOS: HR-1 mice (n = 6) daily for 12 weeks.[117] The mice were exposed to 36 mJ/cm^2 UVB radiation, which was subsequently increased to 54 mJ/cm^2 at weeks 1–4, 72 mJ/cm^2 at weeks 4–7, 108 mJ/cm^2 at weeks 7–10, and finally to 122 mJ/cm^2 at weeks 10–12. No phototoxic effects observed.

The backs of SKH-1 hairless mice (n = 20) were exposed to UV lamps (80% UVB and 20% UVA).[39] The mice were exposed to 90 mJ/cm^2 3 times/week. The dose was increased by 10%/week until the dose reached 175 mJ/cm^2. Treatment stopped at 22 weeks. The experimental groups were (a) untreated control, (b) UV-irradiated control (i.p. with

saline vehicle), (c) red ginseng root extract (25 mg/kg) i.p. in combination with UV-irradiation, (d) UV-irradiated control (topical administration with cream base vehicle), (e) red ginseng root extract topical (0.2%) administration in combination with UV-irradiation. The i.p. injections were administered 24 h prior to each UV irradiation. Topical creams (0.2 mg/cm^2) were applied at least 15 min before UV irradiation. Topical and i.p. treatment with red ginseng root extract reduced the incidence of tumors, reduced tumor multiplicity, and delayed the time of first tumor appearance.

Panax ginseng root extract (extracted with ethanol; 0, 0.5%, 2.5%) was administered in the feed of male SKH-1 hairless mice.[118] The backs of the mice were exposed to UV radiation (~30% UVA) 3 times a week for 12 weeks. The amount of irradiation was progressively increased from 100 mJ/cm^2 per exposure at week 1 (1 minimal erythematous dose = 100 mJ/cm^2) to 400 mJ/cm^2 at week 7. The authors reported a reduction in UV-induced wrinkle formation in both groups fed red ginseng extract compared with animals exposed to UV radiation without ginseng in their feed. No adverse effects were reported in the animals administered ginseng alone.

SAPONINS

Panax ginseng root extract saponin Rb_1 (100 fg,10 pg, and 1 ng/mouse) or 3% vitamin C (1.5 mg/mouse) were applied topically to the dorsal region of male albino hairless HOS: HR-1 mouse (n = 6) every day for 12 weeks.[117] The mice were exposed to 36 mJ/cm^2 UVB, which was subsequently increased to 54 mJ/cm^2 at weeks 1–4, 72 mJ/cm^2 at weeks 4–7, 108 mJ/cm^2 at weeks 7–10, and finally to 122 mJ/cm^2 at weeks 10–12. There were no phototoxic effects observed.

CLINICAL USE

Oral – Human

In multiple efficacy studies of orally administered panax ginseng root extract for treatment or prevention of various maladies, the adverse effects attributable to the extract in placebo-controlled (150 - 11250 mg; Tables 16 and 17), comparative (200 mg; Table 18), and uncontrolled (105 - 4500 mg; Table 19) studies included flu/cold, headache, gastrointestinal complaints, nausea, diarrhea, and vomiting.[66]

GINSENG ABUSE SYNDROME

The characteristic signs and symptoms of overexposure to ginseng, "ginseng abuse syndrome" include morning diarrhea, skin eruptions, sleeplessness, nervousness, and hypertension.[119]

In a study of ginseng abuse syndrome, subjects (n = 133) using ginseng regularly for at least one month were surveyed.[120] It was not possible to differentiate those using panax ginseng and subjects using Siberian ginseng (which is a different genus and species from *Panax ginseng*). Ginseng doses varied from 8 - 10 g 3 times a day for capsules; 0.5 - 3 g twice a day for roots, 1 - 2 g 3 times a day for ground powders, and 2.5 - 5 ml a day for extracts. Most subjects experienced central nervous system excitation and arousal. Fourteen subjects who ingested Panax ginseng roots experienced hypertension, nervousness, sleeplessness, skin eruptions, and morning diarrhea; 5 had edema; 10 became euphoric, restless, agitated, and insomniac. Ten subjects taking high doses (15 g) felt depersonalization and confusion. The average daily dose of ginseng roots was 3 g for persons experiencing ginseng abuse syndrome. One user reported that abrupt withdrawal precipitated hypotension, weakness, and tremor. Ginseng abuse syndrome appeared periodically in the first 12 months of ginseng use but was rarely reported in follow-up examinations at 18 and 24 months. The author suggested that, taken together, these effects mimicked those of corticosteroid poisoning, strongly suggesting a steroidal mechanism of action.

Phytoestrogenic Activity

Summaries of case reports, in vivo, and in vitro studies on phytoestrogenic activity are provided in Table 20.

Several anecdotal reports of ginseng-induced estrogenic activity were discovered. None of these reports identified the origin or source quality, or quantity of the ginseng in the products used by the subjects, or provided sufficient information to enable estimates of the total doses of ginseng to which the patients were exposed. Two of the products contained *Panax ginseng*, one contained Rumanian ginseng (*Eleutherococcus senticosus*; aka Siberian ginseng), and the species of ginseng in the remaining products were not specified. Thus, it is not known whether the latter three products contained Rumanian/Siberian ginseng or other species. The distinction is important because *Eleutherococcus senticosus* does not contain ginsenosides. Other noteworthy unknowns from these reports include the diets, the use of other drugs, and the stress condition of the patients.[121-128]

The available in vivo animal evidence does not support the hypothesis that alcohol extracts of *Panax ginseng* or American ginseng have the potential to act as phytoestrogens. There were no signs of estrogenic activity in rats and mice orally administered up to 5000 mg/kg/d for two years.[129,130]

In vitro experiments using specific, purified ginsenosides, including Rg1, Rb1, and Rh1, showed that these ginsenosides can stimulate signal transduction pathways and produce estrogen receptor (ER)-mediated effects through direct or indirect interaction with ERα or ERβ in cells that express high levels of ERs. However, the crude extracts appear to be much less potent than some of the purified ginsenosides used in the in vitro studies. The potencies of the crude extracts may greatly depend on the extraction method used, and, in some cases, their effects may be attributable to naturally-occurring, non-ginenoside components or impurities, such as mycotoxins, in the extracts.[129,131-144]

In an earlier CIR safety assessment of PEG soy sterols, the report stated that available data on phytosterols are relevant independent of the plant source because of the similarity in structure across plant species.[145] Campesterol,

stigmasterol, and β-sitosterol are the major phytosterol components and among those, β-sitosterol predominates. In this safety assessment, data were available on phytosterol repeat-dose toxicity, estrogenic effects, reproductive toxicity, genotoxicity, and cell proliferation. The Panel noted that phytsterols are poorly absorbed, have little estrogenic activity, and are not reproductive toxicants.

Case Reports

PANAX GINSENG ROOT EXTRACT

A 39-year old man developed hypertension, dizziness, and inability to concentrate during long-term ingestion of ginseng. He stopped taking ginseng, became normotensive within 5 days, and remained normotensive without treatment; after 3 months his symptoms resolved.[146]

A 28-year old woman developed a severe headache after ingesting a large quantity of ethanol-extracted ginseng. Cerebral angiograms showed a "beading" appearance in the anterior and posterior cerebral and superior cerebellar arteries, consistent with cerebral arteritis.[147]

SUMMARY

Ginseng root-derived cosmetic ingredients include: panax ginseng root extract, hydrolyzed ginseng root, hydrolyzed ginseng root extract, hydrolyzed ginseng saponins, panax ginseng root, panax ginseng root powder, panax ginseng root water, panax ginseng root oil, panax ginseng root protoplast, panax japonicus root extract, panax notoginseng root, panax notoginseng root powder, and panax quinquefolium root extract. The cosmetic functions of these ingredients include: skin-conditioning agents - miscellaneous, fragrance ingredients, skin-conditioning agents - miscellaneous, skin conditioning agent-humectant, skin-conditioning agents - emollient, and cosmetic astringent.

If the root is raw or dried, it is referred to as “white” ginseng. If it has been steamed and dried before extraction or pulverizing, it is referred to as “red” ginseng because of a change in coloring. If it is steamed and dried 9 times, the coloring darkens more and the product is referred to as “black ginseng”. The constituents of ginseng roots include: saponins and sapogenins, carbohydrates, organic acids (including amino acids), non-protein nitrogenous substances, peptides, minerals, and enzymes.

The total number of uses of panax ginseng root extract was 149 (102 leave-on products, 42 rinse-off products, and 5 diluted products) at maximum concentrations of 0.000002% – 0.5%. Panax ginseng root was reported to be used in 21 cosmetic products (15 leave-on and 6 rinse-off products). Panax notoginseng root was reported to be used at 0.0004% in rinse off products. Panax quinquefolium root extract was reported to be used in 467 cosmetic products (317 leave-on, 146 rinse-off, and 4 diluted for bath products) at maximum concentrations of 0.002%. There were no uses reported for panax ginseng root powder, hydrolyzed ginseng root, hydrolyzed ginseng root extract, hydrolyzed ginseng saponins, panax ginseng root powder, panax ginseng root water, panax ginseng root oil, panax ginseng root protoplasts, panax japanicus root extract, or panax notoginseng root powder.

There were no dermal, percutaneous, or inhalation toxicokinetic data discovered.

The saponins were poorly absorbed when orally administered as root extract or as individual components.

Panax ginseng root extract was not cytotoxic to human dermal fibroblasts up to 1000 μg/ml.

The acute oral LD_{50} for rats was 750 mg/kg and 200 mg/kg for mice for panax ginseng root. Ginseng root extract had an i.p. LD_{50} 637 mg/kg.

Oral administration of *P. ginseng* root extract was nontoxic to rats up to 5000 mg/kg/d for up to 105 weeks, up to 5000 mg/kg for life for mice, and 15 mg/kg/d for 90 days for dogs.

There were no adverse effects reported in an oral reproductive study at 15 mg/kg/d or a developmental study up to 20 mg/kg/d panax ginseng root extract using rats. In embryo emersion studies using rats and mice, the total morphological scores of embryos exposed to 30 mg/ml of the saponin Rb1 were reduced. The total morphological scores of rat embryos exposed to 30 mg/ml of the saponin Re were reduced. There were no adverse effects to embryos exposed to Rc.

Panax ginseng root extract, up to 75 ppm in feed, did not increase the number of aberrant crypt foci in rat colons. Panax ginseng root extract was not carcinogenic to rats or mice up to 5000 mg/kg for 105 weeks. Panax ginseng root extract, panax ginseng root powder, and panax ginseng quinquefolius root extract were not mutagenic in Ames tests. Panax ginseng saponins were not mutagentic to *S. typhimurium* up to 36 mg/ml.

P. ginseng root extract suppressed TPA-induced skin tumor promotion in mice. Antitumor effects have not been established in humans.

There were case reports of phytoestrogenic activity. In vivo tests did not find estrogenic activity in rats and mice up to 5000 mg/kg/d over 2 years. In vitro experiments showed that Rg1, Rb1, and Rh1 can stimulate signal transduction pathways and produce estrogen receptor-mediated effects through direct or indirect interaction with ERα or ERβ in cells that express high levels of ERs. Extracts were less potent.

Panax ginseng root extract was not irritating to mice up to 0.1% or humans up to 100 mg/ml. Falcarinol at 0.5 mg, Rb1 at 0.05%, Re at 0.05%, Rh1 at 0.05%, Rg5 at 0.05%, Rh3 at 0.05%, Rh2 at 0.1%, Rh3 at 0.1%, Rg3 at 0.05%, Rf at 0.05%, and compound K at 0.05% were not dermally irritating to mice.

There was no sensitivity detected in HRIPTs of products containing Panax ginseng root extract up to 1%.

Panax ginseng root extract was not phototoxic in *C. albicans* assays up to 100%. Panax ginseng root extract was not phototoxic to mice when administered dermally up to 0.2 mg/cm^2, intraperitoneally at 25 mg/kg, or orally up to 2.25%. Dermally applied Rb1 was not phototoxic to mice up to 1 ng/mouse.

In multiple studies of orally administered panax ginseng root extract ranging 105 – 11, 250 mg to test for efficacy for treatment or prevention of various maladies, the adverse effects attributable to the extract in humans included flu/cold, headache, gastrointestinal complaints, nausea, diarrhea, and vomiting.

The characteristic signs and symptoms of overexposure to ginseng, "ginseng abuse syndrome", include morning diarrhea, skin eruptions, sleeplessness, nervousness, and hypertension.

DISCUSSION

Although there are data gaps, the similarity in plant sources, constituents, functions and concentrations in cosmetics allow grouping these ingredients together and interpolating the available toxicological data to support the safety of the entire group.

The Panel expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

While aflatoxin has been detected in the roots of *P. ginseng*, the Panel believes that aflatoxin should not be present in *Panax ginseng* root extract and botanical ingredients that are derived from *P. ginseng*, *P. quinquefolius*, *P. japonicus*, and *P. pseudoginseng*. The Panel expects that the cosmetics industry will use necessary procedures to ensure that ≤ 15 ppb of aflatoxin can be found in cosmetics, as corresponding to "negative" aflatoxin content.

Pulegone is listed as a constituent of *P. quinquefolius*. The Panel recalled that pulegone toxicity was a concern with peppermint oil that required adoption of a concentration limit of ≤ 1% of pulegone. Because of the low use levels of ginseng-derived ingredients, including those derived from *P. quinquefolius*, the Panel was confident that a toxic concentration of pulegone could not be reached in cosmetics. Recent data, for example, reported that *P. quinquefolius* was used at a maximum of 0.002%. The Panel did, however, alert the cosmetics industry that should a ginseng root-derived ingredient be used in a cosmetic product with other botanical ingredients that may contain pulegone, specifically peppermint oil, the total amount of pulegone in the product should not exceed 0.03% for rinse-off products or 0.002% for leave-on products.

The Panel noted that not all of the constituents of *P. japonicus*, *P. notoginseng*, *P. quinquefolium* roots were available as they were for panax ginseng. However, the Panel saw no need for concern due to the similar toxicity data, information on the saponins, and low concentrations of use.

The Panel was concerned about reports in the literature of phytoestrogenic effects of ginseng-related products. After further examination of these reports and other studies, the Panel concluded that attribution to Panax spp,. root products for phytoestrogenic effects is questionable at best. An extensive discussion of the potential estrogenic activity of plant phytosterols had been developed by the Panel for its safety assessment of PEGs soy sterol ingredients. Although no dermal absorption data were available, in the Panel's experience, plant phytosterols and phtosterol esters are not significantly absorbed. Extensive data show that these constituents are not estrogenic, are not reproductive toxicants, are not genotoxic, and are not carcinogenic.

CONCLUSION

The CIR Expert Panel concluded that the following ingredients are safe in the present practices of use and concentration described in this safety assessment:

- panax ginseng root extract
- hydrolyzed ginseng root*
- hydrolyzed ginseng root extract*
- hydrolyzed ginseng saponins*
- panax ginseng root*
- panax ginseng root powder
- panax ginseng root water*
- panax ginseng root oil*
- panax ginseng root protoplast*
- panax japonicus root extract*
- panax notoginseng root
- panax notoginseng root powder*
- panax quinquefolium root extract

Were ingredients in this group not in current use (designated with an asterick*) to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

TABLES AND FIGURES

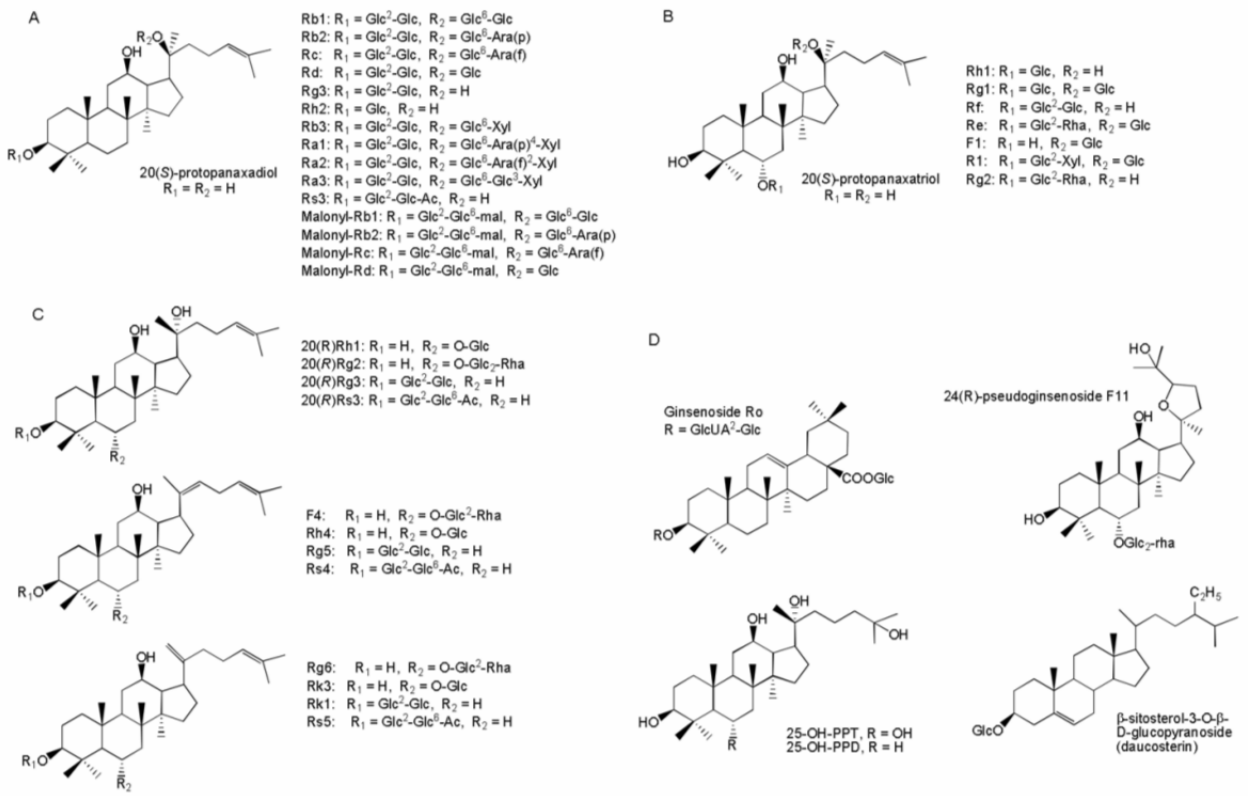

Figure. 1. Structure of selected saponins. **A.** protopanaxadiols (PPD). **B.** protopanaxatriols (PT). **C.** derivatives of PPD and PT. **D.** saponins. Glc, β-D-glucose; Rha, α-L-rhamnose; Ara(p), αL-arabinose(pyranose); Ara(f), α-L-arabinose(furanose); Xyl, β-D-xylose; GlcUA, β-D-glucuronic acid; mal, malonyl; Ac, acetyl.[22]

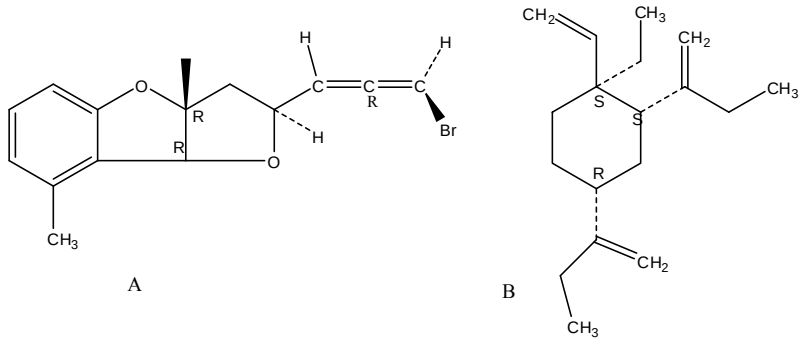

Figure 2. A) Panacene and B) β-elemene.

Table 1. The names, CAS Registry Nos. functions, and definitions of the ginseng root-derived ingredients in this safety assessment.[5]

Ingredient	CAS No.	Function(s)	Definition
Panax Ginseng Root Extract	50647-08-0	Skin-conditioning agents - miscellaneous	The extract of the roots of *Panax ginseng.*
Hydrolyzed Ginseng Root		Skin-conditioning agents - miscellaneous	The hydrolysate of Panax Ginseng Root (q.v.) derived by acid, enzyme or other method of hydrolysis.
Hydrolyzed Ginseng Root Extract		Skin-conditioning agents - miscellaneous	The hydrolysate of Panax Ginseng Root Extract (q.v.) derived by acid, enzyme or other method of hydrolysis.
Panax Ginseng Root	50647-08-0 (generic)	Skin-conditioning agents - miscellaneous	The roots of *P. ginseng*
Panax Ginseng Root Powder	50647-08-0 (generic)	Skin-conditioning agents - miscellaneous	The powder obtained from the dried, ground roots of *P. ginseng.*
Panax Ginseng Root Water	50647-08-0 (generic)	Fragrance ingredients	An aqueous solution of the steam distillate obtained from the roots of *P. ginseng.*
Panax Ginseng Root Oil	50647-08-0 (generic)	Skin-conditioning agents - miscellaneous	The volatile oil obtained from the roots of *P. ginseng.*
Panax ginseng root protoplasts		Skin conditioning agent-humectant	The protoplasts derived from the roots of *P. ginseng.*
Panax japonicus root extract		Skin-conditioning agents - miscellaneous	The extract of the roots and rhizomes of *P. japonicus*
Hydrolyzed Ginseng Saponins		Skin-conditioning agents - emollient	The saponins derived from ginseng that are hydrolyzed by acid, enzyme or other method of hydrolysis.
Panax notoginseng root extract		Skin conditioning agent-humectant	The extract of the roots of *P. notoginseng*
Panax notoginseng root powder		Skin-conditioning agents - miscellaneous	The powder obtained from the dried, ground roots of *P. notoginseng.*
Panax quinquefolium root extract	90045-38-8	Cosmetic astringent	The extract of the roots of *P. quinquefolium.*

Table 2. Physical and chemical properties of ginseng root ingredients.

Property	Value	Reference
Panax ginseng root extract (red ginseng)		
Color	Pale yellow	12
Odor	Typical	12
pH (10% solution)	4.0-7.0	12
Specific gravity	0.980-1.100	12
Hydrolyzed ginseng root		
Odor	Characteristic	148
Hydrolyzed ginseng root extract		
None found		
Hydrolyzed ginseng saponins		
None found		
Panax ginseng root		
Physical Form	Powder	148,149
Color	Yellowish white	148,149
Panax ginseng root powder		
Physical form	Powder	148
Color	Light yellowish white to light yellowish brown	148
Odor	Characteristic	148
Panax ginseng root water		
None found		
Panax ginseng root oil		
Physical Form	Oil	44
Color	Pale white	44
Panax ginseng root protoplast		
None found		
Panax japonicus root extract		
None found		

Table 2. Physical and chemical properties of ginseng root ingredients.

Property	Value	Reference
Panax nonoginseng root		
None found		
Panax notoginseng root powder		
None found		
Panax quinquefolium root extract		
	Liquid	12
Color	Pale yellow	12
Odor	Typical	12
Specific gravity	0.980-1.100	12
Solubility in water	Soluble	12
pH (10% aqueous)	4.0-7.0	12

Table 3. Physical and chemical properties of saponins.

Property	Value	Reference
Ro		
Physical Form	Needles	150
Color	Colorless	150
Melting Point ºC	239-241	150
Rb1		
Physical Form	Powder	150
Color	White	150
Melting Point ºC	197-198	150
Rb2		
Physical Form	Powder	150
Color	White	150
Melting Point ºC	200-203	150
Rc		
Physical Form	Powder	150
Color	White	150
Melting Point ºC	199-201	150
Rd		
Physical Form	Powder	150
Color	White	150
Melting Point ºC	206-209	150
Re		
Physical Form	Needles	151
Color	Colorless	151
Melting Point ºC	201-203	151
Rf		
Physical Form	Powder	151
Color	White	151
Melting Point ºC	197-198	151
Rg1		
Physical Form	Powder	151
Color	Colorless	151
Boiling Point ºC	194-196	151
Rg2		
Physical Form	Powder	151
Color	Colorless	151
Melting Point ºC	187-189	151

Table 4. Chemical constituents of *Panax ginseng* root.[17]

Constituent	Part	Lo (ppm)	Hi (ppm)
(-)-Beta-panasinsene	Root Essent. Oil		
1,8-cineol	Root Essent. Oil		
10-acetyl-panaxytriol	Root		
1-o-alpha-glucoside-propan-2-on-1-ol	Root		
20-(s)-dihydro-protopanaxatrione	Root		
20(s)-protopanaxadiol-3-o-beta-d-glucopyranoside	Root		10
20-glucosyl-ginsenoside	Root		50
20(r)-ginsenoside-rh-1	Rhizome		
2-5-dimethyl-tridecane	Root Essent. Oil		
2-6-diethyl-pyrazine	Root		
2-6-ditert-butyl-4-methyl-phenol	Root Essent. Oil		14000
2-ethyl-5-methyl-pyrazine	Root		
2-ethyl-6-methyl-pyrazine	Root		
2-glucoginsenoside-rf	Root		50
2-iso-butyl-3-methoxy-pyrazine	Root		
2-iso-propyl-3-methoxy-pyrazine	Root		
2-iso-propyl-5-methyl-anisole	Root		
2-methyl-hexanoic-acid-ehtyl-ester	Root		
2-methyl-tetradecane	Root Essent. Oil		29000
2-sec-butyl-3-methoxy-pyrazine	Root		
3-9-10-triacetoxy-heptadeca-1-16-diene-4-6-diyne	Root		
3-iso-propyl-2-methoxy-5-methyl-pyrazine	Root		
3-sec-butyl-2-methoxy-5-methyl-pyrazine	Root		
4-methyl-thiazole-5-ethanol	Root		
4-oxy-oct-6-enoic-acid-methyl-ester	Root		
5-ethyl-2-3-dimethyl-pyrazine	Root		
9-10-epoxy-heptadec-1-16-diene-4-6-diyn-3-one	Root		
9-10-epoxy-heptadeca-1-16-diene-4-6-diyn	Root		
Acetyl-panaxydol	Root		2.1
Adenine	Root		
Adenosine	Root		90
Adenosine	Rhizome		
Adenyl-cyclase	Root		
Alanine	Root		
Allo-aromadendrene	Root Essent. Oil		
Alpha-amylase	Root		
Alpha-fructose	Root		
Alpha-gamma-dipalmitin	Root		
Alpha-glucose	Root		
Alpha-guaiene	Root		
Alpha-guaiene	Root Essent. Oil		40000
Alpha-humulene	Root Essent. Oil		
Alpha-maltose	Root		
Alpha-maltosyl-beta-d-fructofuranoside	Root		
Alpha-neoclovene	Root Essent. Oil		
Alpha-panasinsene	Root		17.6
Alpha-panasinsene	Root Essent. Oil		
Alpha-phellandrene	Root		
Alpha-phellandrene	Root Essent. Oil		
Alpha-pinene	Root		
Alpha-pinene	Root Essent. Oil		
Alpha-pyrrolidone	Root		
Alpha-santalene	Root Essent. Oil		
Alpha-selinene	Root Essent. Oil		
Aluminum	Root	5	22
Amino-acids	Root		
Arachidic acid	Root		

Table 4. Chemical constituents of *Panax ginseng* root.[17]

Constituent	Part	Lo (ppm)	Hi (ppm)
Arginine	Root		
Aromadendrene	Root Essent. Oil		
Arsenic	Root		
Ascorbic-acid	Root		0
Ash	Root	10600	50000
Aspartase	Root		
Aspartic-acid	Root		
Behenic-acid	Root		
Benzyl-beta-primeveroside	Root		47
Beta-amylase	Root		
Beta-bisabolene	Root Essent. Oil		
Beta-carotene	Root		
Beta-elemene	Root		
Beta-elemene	Root Essent. Oil		150000
Beta-eudesmol	Root Essent. Oil		
Beta-farnesene	Root		
Beta-farnesene	Root Essent. Oil		85000
Beta-fructose	Root		
Beta-glucose	Root		
Beta-guaiene	Root Essent. Oil		
Beta-gurjunene	Root Essent. Oil	60000	10,503
Beta-humulene	Root Essent. Oil		
Beta-maaliene	Root		
Beta-maltose	Root		
Beta-neoclovene	Root Essent. Oil		
Beta-panasinsene	Root		10.2
Beta-patchoulene	Root		
Beta-patchoulene	Root Essent. Oil		
Beta-selinene	Root Essent. Oil		80000
Beta-sitosterol	Root		
Beta-sitosterol	Rhizome		
Beta-sitosterol-3-o-beta-d-glucoside	Root		
Bicyclogermacrene	Root		
Biotin	Root		0.9
Caffeic acid	Root		
Calcium	Root	611	4140
Campesterol	Root		
Campesterol-6'-linolenylglucoside	Root		
Campesterol-6'-linolylglucoside	Root		
Campesterol-6'-oleylglucoside	Root		
Campesterol-6'-palmitylglucoside	Root		
Campesterol-6'-stearylglucoside	Root		
Caproic-acid-butyl-ester	Root		
Caproic-acid-propyl-ester	Root		
Carbohydrates	Root	176808	834000
Carbon-disulfide	Root		1500
Caryophyllene	Root Essent. Oil		
Caryophyllene alcohol	Root Essent. Oil		
Catalase	Root		
Cellulase	Root		
Cerebroside	Root		
Choline	Root	1000	2000
Chromium	Root	0.2	1.1
Chromium	Root		1.1
Cis-caryophyllene	Root Essent. Oil		
Citral	Root		
Citral	Root Essent. Oil		
Citric-acid	Root		
Cobalt	Root	0.7	3.1

Table 4. Chemical constituents of *Panax ginseng* root.[17]

Constituent	Part	Lo (ppm)	Hi (ppm)
Cobalt	Root		3.1
Copper	Root		17
Cysteine	Root		
Cystine	Root		
Daucosterine	Root		
Daucosterol	Root		
Daucosterol	Rhizome		
Delta-cadinene	Root		
Densichine	Root		
D-fructose	Root		
D-glucose	Root		
Diglycosyl diglyceride	Root		
Di-iso-propyl-sulfide	Root		
Disaccharides	Root		33000
D-sucrose	Root		
Elemene	Root		
Eo	Root	100	500
Epsilon muurolene	Root Essent. Oil		
Eremophilene	Root Essent. Oil		23000
Erucic-acid	Root		
Estradiol	Root		
Estriol	Root		
Estrone	Root		
Eugenol	Root Essent. Oil		
Falcarinol	Root	0.9	310
Falcarinol	Rhizome		
Fat	Root	3752	17700
Ferulic-acid	Root		
Fiber(crude)	Root		72000
Fiber(dietary)	Root		301000
Fluoride	Root		26.3
Folic-acid	Root		
Fructose	Root	200	6000
Fumaric-acid	Root		
Gadoleic-acid	Root		
Galactose	Root		
Galanin	Root		
Gamma aminobutyric acid	Root		
Gamma-elemene	Root Essent. Oil	60000	100000
Gamma-patchoulene	Root Essent. Oil		
Gamma-selinene	Root Essent. Oil		
Ge	Root		
GENSENOSIDE RD [sic]	Root		
Gentisic-acid	Root		
Germanium	Root	0.12	320
Ginsenan-pa	Root		235
Ginsenan-pb	Root		170
Ginsenan-s-i-a	Root		106.6
Ginsenan-s-ii-a	Root		90
Ginseng-polypeptide	Root		
Ginseng-polypeptide-gpp	Root		
Ginsenol	Root		9.6
Ginsenoside	Root		47000
Ginsenoside-k	Root		
Ginsenoside-ng-r-2	Root		
Ginsenoside-ra	Root	100	300
Ginsenoside-ra-1	Root	100	300
Ginsenoside-ra-2	Root		300
Ginsenoside-ra-3	Root		50

Table 4. Chemical constituents of *Panax ginseng* root.[17]

Constituent	Part	Lo (ppm)	Hi (ppm)
Ginsenoside-ra-o	Root		
Ginsenoside-rb	Root	11300	40000
Ginsenoside-rb	Rhizome		
Ginsenoside-rb-1	Root	1700	83000
Ginsenoside-rb-1	Rhizome	8800	14,000
Ginsenoside-rb-1	Root Bark		
Ginsenoside-rb-2	Root	100	23000
Ginsenoside-rb-2	Root Bark		
Ginsenoside-rb-2	Rhizome	4500	5700
Ginsenoside-rb-2-c	Root		
Ginsenoside-rb-3	Root		50
Ginsenoside-rb-c	Root		14000
Ginsenoside-rb-c	Root Bark		24000
Ginsenoside-rb-group	Root		
Ginsenoside-rc	Root	500	25000
Ginsenoside-rc	Root Bark		
Ginsenoside-rc	Rhizome		4700
Ginsenoside-rc-2	Root		
Ginsenoside-rd	Root	380	21200
Ginsenoside-rd	Root Bark		
Ginsenoside-rd	Rhizome	700	1600
Ginsenoside-rd-2	Root		
Ginsenoside-re	Root	680	84800
Ginsenoside-re	Rhizome	4700	5700
Ginsenoside-re-2	Root		
Ginsenoside-re-3	Root		
Ginsenoside-rf	Root	200	9200
Ginsenoside-rf	Rhizome		1500
Ginsenoside-rg	Root	4600	16300
Ginsenoside-rg	Root Bark		34000
Ginsenoside-rg-1	Root	320	58400
Ginsenoside-rg-1	Root Bark		
Ginsenoside-rg-1	Rhizome	3800	4500
Ginsenoside-rg-2	Root	100	26700
Ginsenoside-rg-2	Rhizome		
Ginsenoside-rg-3	Root	3	30
Ginsenoside-rh	Root		
Ginsenoside-rh1	Root		15
Ginsenoside-rh-2	Root		
Ginsenoside-r-o	Root	100	11000
Ginsenoside-r-o	Rhizome	18,000	34,000
Ginsenosides	Root	10720	30000
Ginsenoside-z-r-1	Root		
Ginsenoyne-a	Root		12.8
Ginsenoyne-a-linoleate	Root		2.8
Ginsenoyne-b	Root		1.5
Ginsenoyne-c	Root		1.1
Ginsenoyne-d	Root		7.1
Ginsenoyne-e	Root		7.1
Ginsenoyne-f	Root		2.6
Ginsenoyne-g	Root		0.176
Ginsenoyne-h	Root		1.47
Ginsenoyne-i	Root		2.6
Ginsenoyne-j	Root		3.5
Ginsenoyne-k	Root		14.1
Ginsenoynes	Root		
Glucose	Root	100	9000
Glutamic-acid	Root		
Gly-arg-gamma-glu-val-nh2	Root		

Table 4. Chemical constituents of *Panax ginseng* root.[17]

Constituent	Part	Lo (ppm)	Hi (ppm)
Glycine	Root		
Glyco-chenodeoxycholic-acid	Root		
Glycocholic-acid	Root		
Glyco-deoxy-cholic-acid	Root		
Gomsempsode-rb-2	Root		
Guanine	Root		
Gum	Root	27560	130000
Harman	Root		
Heneicosanoic-acid	Root		
Heptadec-1-en-4,6-diyn-3,9,10-triol	Root		
Heptadec-1-en-4,6-diyne-3,9,10-triol	Root		
Heptadec-1-en-4,6-diyne-3,9-diol	Root		150
Heptadeca-1-4-diene-6-8-diyne-3-10-diol	Root		
Heptadeca-1-8-diene-4-6-diyn-3-10-diol	Root		
Heptadeca-1-8-diene-4-6-diyn-10-ol-3-one	Root		
Heptadeca-1-8-diene-4-6-diyn-3-10-dione	Root		
Heptadeca-1-8-diene-4-6-diyne-3-10-diol	Root		14.6
Heptadeca-1-9-diene-4-6-diyn-3-ol	Root		
Heptadeca-1-en-4,6-diyn-3,9-diol	Root		150
Heptadeca-1-ene-4-6-diyne-3-9-10-triol	Root		1.5
Heptadeca-1-trans-8-diene-4-6-diyne-3-10-diol	Root		5.2
Heptadecan-1-ol	Root Essent. Oil		19000
Heptadecan-2-one	Root Essent. Oil		43000
Heptadecanoic-acid	Root		
Histidine	Root		20
Humulene	Root Essent. Oil		24000
Invertase	Root		
Iron	Root		180
Iso-butyl-propionate	Root		
Isoleucine	Root		
Iso-propyl-propionate	Root		
Karusan-a	Root		
Karusan-b	Root		
Karusan-c	Root		
Karusan-d	Root		
Karusan-e	Root		
Ketoglutaric acid	Root		
Kilocalories	Root		2740
Leucine	Root		
Lignoceric acid	Root		
Ligustrazine	Root		
Limonene	Root		
Limonene	Root Essent. Oil		
Linalool	Root Essent. Oil		
Linoleic acid	Root		140
Linolein	Root		
Linolenic acid	Root		
Lysine	Root		
Lysophosphatidylcholine	Root		
Lysophosphatidyl-inositol	Root		
Magnesium	Root	102	1950
Maleic acid	Root		
Malic acid	Root		
Malonyl-ginsenoside-rb-1	Root	2730	13000
Malonyl-ginsenoside-rb-1	Rhizome	6900	13,000
Malonyl-ginsenoside-rb-2	Root	1370	11000
Malonyl-ginsenoside-rb-2	Rhizome	4000	4200
Malonyl-ginsenoside-rc	Root	1000	8400
Malonyl-ginsenoside-rc	Rhizome	3400	3500

Table 4. Chemical constituents of *Panax ginseng* root.[17]

Constituent	Part	Lo (ppm)	Hi (ppm)
Malonyl-ginsenoside-rd	Root	400	1200
Malonyl-ginsenoside-rd	Rhizome		
Maltol	Root		
Maltose	Root	5100	199600
Manganese	Root	0.4	180
Mannitol	Root		
Mayurone	Root Essent. Oil		
Methionine	Root		
Molybdenum	Root		
Monosaccharides	Root		15000
Myristic-acid	Root		
N-9-formyl-harman	Root		0.1
Nervonic acid	Root		
N-formyl-harman	Root		
Niacin	Root	17	80
Nicotinamide	Root		
Nicotinic acid	Root		
N-nonacosane	Root		
N-nonacosane	Rhizome		
Norharman	Root		
Notoginsenoside-r-1	Root		20
N-pentadecane	Root Essent. Oil		18000
O-alpha-d-glucopyranosyl...fructofuranoside	Root		
O-alpha-d-glucopyranosyl...glucopyranose	Root		
Oleanolic acid	Root	150	700
Oleic acid	Root		
Oxalic acid ethyl ester	Root		
Palmitic-acid	Root Essent. Oil		86000
Palmitoleic-acid	Root		
Panacene	Root		
Panasinsanol-a	Root		2.3
Panasinsanol-b	Root		12.5
Panaxacol	Root		
Panaxadiol	Root	700	6500
Panaxan-a	Root		
Panaxan-b	Root		
Panaxan-c	Root		
Panaxan-d	Root		
Panaxan-e	Root		
Panaxan-f	Root		
Panaxan-g	Root		
Panaxan-h	Root		
Panaxan-i	Root		
Panaxan-j	Root		
Panaxan-k	Root		
Panaxan-l	Root		
Panaxan-m	Root		
Panaxan-n	Root		
Panaxan-o	Root		
Panaxan-p	Root		
Panaxan-q	Root		
Panaxan-r	Root		
Panaxan-s	Root		
Panaxan-t	Root		
Panaxan-u	Root		
Panaxatriol	Root	700	7700
Panaxatriol-glycoside	Root		
Panax-ginseng-20(s)-prosapogenin	Root		
Panax-ginseng-genin-f-1	Root		

Table 4. Chemical constituents of *Panax ginseng* root.[17]

Constituent	Part	Lo (ppm)	Hi (ppm)
Panax-ginseng-genin-f-2	Root		
Panax-ginseng-genin-f-4	Root		
Panax-ginseng-glycoprotein	Root		
Panax-ginseng-glycoside-p-1	Root		
Panax-ginseng-lipolytic-peptide	Root		
Panax-ginseng-polyacetylene-c	Root		
Panax-ginseng-polyacetylene-d	Root		
Panax-ginseng-polyacetylene-e	Root		
Panax-ginseng-polyacetylene-f	Root		
Panax-ginseng-polyacetylene-g	Root		
Panax-ginseng-protein	Root		
Panax glycoprotein	Root		
Panaxic acid	Root		
Panaxin	Root		
Panaxoside-a	Root		
Panaxoside-a-progenin-i	Root		
Panaxoside-b	Root		
Panaxoside-c	Root		
Panaxoside-d	Root		
Panaxoside-e	Root		
Panaxoside-f	Root		
Panax-polypeptide	Root		
Panax-polyphenolic-permethyl-ether	Root		
Panax-polysaccharide	Root	30000	40000
Panax-polysaccharide-gh-1	Root		
Panax-polysaccharide-gl-4	Root		
Panax-polysaccharide-gl-4-ii-b-1-ii	Root		
Panax-protein	Root		
Panax-saponin-a	Root		
Panax-saponin-c	Root		
Panaxydol	Root	357.1	440
Panaxydol-chlorohydrin	Root		13.5
Panaxydol-linoleate	Root		8.1
Panaxyne	Root		
Panaxyne-epoxide	Root	1.8	9
Panaxynol	Root		
Panaxynol-linoleate	Root		1.3
Panaxytriol	Root	14.2	250
Pantothenic-acid	Root		6.6
Patchoulene	Root Essent. Oil		20000
P-coumaric-acid	Root		
Pectin	Root		
Pentadecanoic acid	Root		
Perlargonidin-3-o-beta-d-glucoside	Root		
Perlolyrine	Root		1.6
Phenolase	Root		
Phenylalanine	Root		
Phosphatidic-acid	Root		
Phosphatidyl-choline	Root		
Phosphatidyl-ethanolamine	Root		
Phosphatidyl-glycerol	Root		
Phosphatidyl-inositol	Root		
Phosphorus	Root	112	528
P-hydroxycinnamic-acid	Root		26
Polyacetylenes	Root		
Polysaccharide	Root		
Polysaccharide	Rhizome		
Polysaccharide-sa	Root		
Polysaccharide-sb	Root		

Table 4. Chemical constituents of *Panax ginseng* root.[17]

Constituent	Part	Lo (ppm)	Hi (ppm)
Potassium	Root	515	10700
Proline	Root		
Pro-renin	Root		
Protein	Root	23108	109000
Protopanaxadiol	Root		
Protopanaxadiol-glycosides	Root		
Putrescine	Root		
Pyroglutamic-acid	Root		
Pyruvic acid	Root		
Quinquenoside-r-1	Root		20
Rhamnose	Root		
Riboflavin	Root	0.4	1.8
Salicylic-acid	Root		3.4
Saponin-ii	Root		
Saponin-iii	Root		
Saponin-iv	Root		
Saponins	Root		20000
Saponin-v	Root		
Selenium	Root	0.5	2.5
Selina-4(14),7(11)-diene	Root Essent. Oil		
Senecrassidiol	Root		
Serine	Root		
Sesquiterpenediol	Root		
Silicon	Root		
Sitosterol-6'-linolenylglucoside	Root		
Sitosterol-6'-linolylglucoside	Root		
Sitosterol-6'-oleylglucoside	Root		
Sitosterol-6'-palmitylglucoside	Root		
Sitosterol-6'-stearylglucoside	Root		
Sodium	Root	5	209
Spermidine	Root		
Spinacine	Root		33.3
Starch	Root	25440	320000
Starch	Rhizome		
Stearic acid	Root		
Stigmasterol	Root		
Stigmasterol-6'-linolenylglucoside	Root		
Stigmasterol-6'-linolylglucoside	Root		
Stigmasterol-6'-oleylglucoside	Root		
Stigmasterol-6'-palmitylglucoside	Root		
Stigmasterol-6'-stearylglucoside	Root		
Succinic acid	Root		
Sucrose	Root	1300	226000
Sucrose	Rhizome		
Sugars	Root	19080	90000
Superoxide dismutase	Root		
Tartaric-acid	Root		
Terpineol	Root		
Terpineol	Root Essent. Oil		
Thiamine	Root	0.4	1.7
Threonine	Root		
Thuj-4(10)-ene	Root		
Tin	Root	3.4	16
Trace-elements	Root		
Trans-beta-farnesene	Root Essent. Oil		80000
Trans-caryophyllene	Root Essent. Oil		
Tricosanoic-acid	Root		
Trimethyl-pyrazine	Root		
Tripalmitin	Root		

Table 4. Chemical constituents of *Panax ginseng* root.[17]

Constituent	Part	Lo (ppm)	Hi (ppm)
Tyrosine	Root		
Uracil	Root		
Uridine	Root		
Valine	Root		
Vanillic-acid	Root		55
Vitamin-b12	Root		
Water	Root		788000
Xylose	Root		
Zinc	Root		27

Table 5. Chemical constituents of *P. quinquefolius* root.[18]

Constituent	Plant Part	Lo (ppm)	Hi (ppm)
1-2-9-10-diepoxy-3-oxo-heptadeca-4-6-diyne	Root		1.7
1-hydroxy-9-10-epoxy-c-oxo-heptadeca-4-6-diyne	Root		7.1
2-phenyl-dodecane	Root Essent. Oil		41500
3-phenyl-dodecane	Root Essent. Oil		16700
3-phenyl-undecane	Root Essent. Oil		16700
4-phenyl-dodecane	Root Essent. Oil		15600
6(r),7(s)-epoxy-tetradeca-1,3-diyne	Root		
6-7-epoxy-tetradeca-1-3-dien	Root		2.8
8-acetoxy-9,10-epoxyheptadeca-4,6-diyn-1-en-3-ol	Root		2.2
Acetyl-panaxydol	Root		2.8
Alpha-caryophyllene-alcohol	Root Essent. Oil	1457	23135
Alpha-curcumene	Root Essent. Oil	1626	8677
Alpha-elemene	Root Essent. Oil	3352	19550
Alpha-fructose	Root		
Alpha-glucose	Root		
Alpha-maltose	Root		
Alpha-muurolene	Root Essent. Oil	2007	9855
Amino-acids	Root		
Beta-bisabolene	Root Essent. Oil	6251	58670
Beta-cubebene	Root Essent. Oil	997	13216
Beta-farnesene	Root Essent. Oil		260500
Beta-fructose	Root		
Beta-glucose	Root		
Beta-gurjunene	Root Essent. Oil	4908	78900
Beta-maaliene	Root Essent. Oil	4938	6134
Beta-maltose	Root		
Beta-n-oxalo-l-alpha-beta-diaminopropionic-acid	Root		200
Beta-sitosterol	Root		
Caproic-acid	Root Essent. Oil		28600
Caryophyllene	Root Essent. Oil		8670
Cis-beta-farnesene	Root Essent. Oil	4961	5279
Dibutyl-phthalate	Root Essent. Oil	9860	29274
D-sucrose	Root		
Elemol	Root Essent. Oil	2959	14637
Eo	Root		
Falcalinol	Root		558.3
Fructose	Root		3400
Galactose	Root		
Ginsenoside-a-1	Root		
Ginsenoside-f2	Root		180
Ginsenoside-frc	Root		
Ginsenoside-rb-1	Rhizome		
Ginsenoside-rb-1	Root	270	20900
Ginsenoside-rb-2	Rhizome		
Ginsenoside-rb-2	Root	200	1000
Ginsenoside-rb-3	Root		300
Ginsenoside-rc	Rhizome		
Ginsenoside-rc	Root	630	3100
Ginsenoside-rd	Rhizome		
Ginsenoside-rd	Root	950	7700

Table 5. Chemical constituents of *P. quinquefolius* root.[18]

Constituent	Plant Part	Lo (ppm)	Hi (ppm)
Ginsenoside-rd-1	Root	3400	3700
Ginsenoside-re	Root	200	13800
Ginsenoside-re-2	Root		
Ginsenoside-re-3	Root		
Ginsenoside-rf	Root		
Ginsenoside-rg	Root		
Ginsenoside-rg-1	Rhizome		
Ginsenoside-rg-1	Root	300	8600
Ginsenoside-rg-2	Root		80
Ginsenoside-rg-3	Root		
Ginsenoside-rh1	Rhizome		9800
Ginsenoside-rh1	Root		
Ginsenoside-rh-2	Rhizome		18600
Ginsenoside-rh-2	Root		
Ginsenoside-r-o	Rhizome		
Ginsenoside-r-o	Root	700	1000
Ginsenosides	Root	24400	38800
Ginsenoyne-g	Root		5.7
Glucose	Root		3200
Guaiol	Root Essent. Oil	4649	11276
Gypenoside-f-11	Root		
Gypenoside-xvii	Root		300
Heptadeca-1-8-diene-4-6-diyne-3-10-diol	Root		15
Ledol	Root Essent. Oil	6831	7680
Malonyl-ginsenoside-rb-1	Rhizome		
Malonyl-ginsenoside-rb-1	Root		
Malonyl-ginsenoside-rb-2	Rhizome		
Malonyl-ginsenoside-rb-2	Root		
Malonyl-ginsenoside-rc	Rhizome		
Malonyl-ginsenoside-rc	Root		
Malonyl-ginsenoside-rd	Rhizome		
Malonyl-ginsenoside-rd	Root		
Maltose	Root		3800
Myristic-acid	Root		
N-hexadecane	Root Essent. Oil		88900
Nonadecadienoic-acid-methyl-ester	Root Essent. Oil	27682	37935
Octadecadienoic-acid-methyl-ester	Root Essent. Oil	13701	56439
Oleanolic-acid	Root	600	980
Oleic-acid	Root		
Palmitic-acid	Root		
Palmitic-acid	Root Essent. Oil	6543	41917
Palmitic-acid-ethyl-ester	Root Essent. Oil	35913	73504
Palmitic-acid-methyl-ester	Root Essent. Oil	16744	63486
Panaquilin-e-1	Root		
Panaquilin-g-2	Root		
Panaxadiol	Root	3100	9600
Panaxan-a	Root		
Panaxan-b	Root		
Panaxan-c	Root		
Panaxan-d	Root		
Panaxan-e	Root		
Panaxatriol	Root	1500	12540
Panax-polyacetylene-pq-1	Root		75.8
Panax-polyacetylene-pq-2	Root		6.6
Panax-polyacetylene-pq-3	Root		29.1
Panax-protein	Root		
Panaxydol	Root		950
Panaxytriol	Root		59.1
Protein	Root	80600	102500
Pseudo-ginsenoside-f-11	Root	70	400
Pulegone	Root Essent. Oil		260500
Quinquefolan-a	Root		
Quinquefolan-b	Root		
Quinquefolan-c	Root		
Quinquenoside-r-1	Root		100
Saponins	Root		
Stigmasterol	Root		
Sucrose	Root	39000	158600
Superoxide-dismutase	Root		
Trans-beta-farnesene	Root Essent. Oil	9768	63517

Table 5. Chemical constituents of *P. quinquefolius* root.[18]

Constituent	Plant Part	Lo (ppm)	Hi (ppm)
Xylose	Root		

Table 6. Chemical constituents of *P. japonicus* root (rhizome).[20]

Constituent	Amount (ppm)
Arabinose	
Beta sitosterol	
Calcium	7000
Campesterol	
Campesterol-6'-linolenylglucoside	
Campesterol-6'-linoylglucoside	
Campesterol-6'-oleylglucoside	
Campesterol-6'-palmitylglucoside	
Campesterol-6'-stearylglucoside	
Chikusetsusaponin-I-A	
Chikusetsusaponin-I-B	
Chikusetsusaponin-III	
Chikusetsusaponin-IV	
Chikusetsusaponin-IV-A	1900
Copper	6
Ginsenoside-R-O	
Ginsenoside-RD	6700
Ginsenoside-RG-2	
Glucose	
Glucuronic acid	
Iron	360
Magnesium	2400
Majonoside-R1	700
Majonoside-R2	1100
Manganese	43
Notoginsenoside-R2	300
Oleanolic acid	
Panatoxin	
Potassium	11000
Saponins	70000
Sitosetrol-6'-stearylglucoside	
Sitosetrol-6'-linolenylglucoside	
Sitosetrol-6'-linolylglucoside	
Sitosetrol-6'-oleylglucoside	
Sodium	499
Stigmasterol-6'-linolenylglucoside	
Stigmasterol-6'-linolylglucoside	
Stigmasterol-6'-oleylglucoside	
Stigmasterol-6'-palmitylglucoside	
Stigmasterol-6'-stearylglucoside	
Zinc	20

Table 7. Chemical constituents of *P. pseudoginseng* (*notoginseng*) root.[19]

Constituent	Amount (ppm)
(20)-Protopanoxadiol	
(20)-Protopanoxatiiol	
Beta sitosterol	
Daucosterol	
Ginsenoside RA	
Ginsenoside RA	
Ginsenoside RB	
Ginsenoside RB-1	
Ginsenoside RB-2	
Ginsenoside RE	
Ginsenoside RG-1	
Ginsenoside RG-2	
Ginsenosides	87000
Notogenisnosides	
Panaxynal	
Quercetin	

Table 8. Comparison of saponin content between white (dried, unsteamed) and black (steamed and dried 9 times) ginseng extract (extracted with 80% ethanol).[9]

Saponin	White ginseng extract (mg/g)	Black ginseng extract (mg/g)
Rg1	7.81 ± 4.83	Not detected
Re	9.30 ± 0.88	Not detected
Rh1	0.74 ± 0.31	0.67 ± 0.15
Rb1	14.14 ± 1.35	2.96 ± 1.60
Rc	12.62 ± 3.02	1.61 ± 0.71
Rb2	6.97 ± 1.48	0.63 ± 0.21
Rd	2.88 ± 1.37	0.53 ± 0.44
Rg3(R)	Not detected	5.80 ± 1.42
Rg3(S)	Not detected	1.97 ± 0.53
Total	54.45 ± 5.08	14.17 ± 4.33

Table 9. Comparison of saponin content in *P. ginseng* root by extraction technique.[11,14]

Saponin	**Content (%)**	
	3 batches of hydro-glycolic extract	**Ultrahypothermia biotic extract**
Rg1	0.004-0.02	4.17
Re	Below 0.03[1]	18.99
Rf	NR	1.87
Rb1	0.05-0.06	34.49
Rg2	NR	2.30
Rh1	NR	13.31
Rc	Below 0.02[1]	-
Rb2	0.02-0.04	5.08
Rb3	NR	3.37
Rd	Below 0.02[1]	14.89
Rg3	NR	-
Rh2	NR	1.52

[1] Detection limit.
NR – Not reported

Table 10. Frequency and concentration of use of panax spp. root-derived ingredients as well as use concentration of white and red panax ginseng root extract according to duration and type of exposure.[152,153] There were no reported uses for hydrolyzed ginseng root, hydrolyzed ginseng root extract, hydrolyzed ginseng saponins, panax ginseng root, panax ginseng root water, panax ginseng root oil, panax ginseng root protoplast, panax japonicus root extract, and panax notoginseng root powder.

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Panax ginseng root extract[1]		**Panax ginseng root**		**Panax notoginseng root**		**Panax quinquefolium root extract**	
Total/range	**277**	**0.000002-0.5**	**22**	NR	NR	**0.0004**	**430**	**0.0005-0.002**
Duration of use								
Leave-on	196	0.000002-0.5	16	NR	NR	NR	286	NR
Rinse-off	77	0.00000-0.3	6	NR	NR	0.0004	140	0.0005-0.002
Diluted for (bath) use	4	0.00004-0.0004	NR	NR	NR	NR	4	NR
Exposure type								
Eye area	30	0.00001-0.1	2	NR	NR	NR	30	NR
Incidental ingestion	4	0.0001-0.1	NR	NR	NR	0.0004	8	NR
Incidental Inhalation-sprays	10	0.00005-0.1[2]	2	NR	NR	NR	16	NR
Incidental inhalation-powders	6	0.0004-0.01	NR	NR	NR	NR	7	NR
Dermal contact	224	0.000003-0.5	17	NR	NR	NR	316	0.002
Deodorant (underarm)	NR	0.02	2	NR	NR	NR	2	NR
Hair-noncoloring	47	0.000002-0.3[3]	5	NR	NR	NR	97	0.0005
Hair-coloring	NR	0.0002-0.005	NR	NR	NR	NR	7	NR
Nail	NR	0.00001-0.1	NR	NR	NR	NR	1	NR
Mucous Membrane	25	0.00004-0.1	1	NR	NR	0.0004	40	0.002
Baby	NR	NR	NR	NR	NR	NR	NR	NR

	Panax ginseng root powder		**White Panax ginseng root extract**		**Red Panax ginseng root extract**		
Total/range	**1**	NR	NS	**0.00009-0.04**	NS	**0.00004-0.003**	
Duration of use							
Leave-on	NR	NR	NS	0.0003-0.04	NS	0.00004-0.003	
Rinse-off	1	NR	NS	0.0003	NS	0.003	
Diluted for (bath) use	NR	NR	NS	0.00009	NS	NR	
Exposure type							
Eye area	NR	NR	NS	0.002	NS	NR	
Incidental ingestion	NR	NR	NS	NR	NS	NR	
Incidental Inhalation-sprays	NR	NR	NS	NR	NS	0.00004	
Incidental inhalation-powders	NR	NR	NS	0.0003	NS	NR	
Dermal contact	1	NR	NS	0.00009-0.04	NS	0.00004-0.003	
Deodorant (underarm)	NR	NR	NS	NR	NS	NR	
Hair-noncoloring	NR	NR	NS	0.0003	NS	0.003	
Hair-coloring	NR	NR	NS	NR	NS	NR	
Nail	NR	NR	NS	NR	NS	NR	
Mucous Membrane	NR	NR	NS	0.00009	NS	NR	
Baby	NR	NR	NS	NR	NS	NR	

[1] The VCRP listed Panax ginseng root extract and ginseng extract as separate ingredients. These were combined under Panax ginseng root extract.
[2] It is not known if this product is a spray.
[3] 0.3% in a rinse-off non-coloring other hair preparation.
NR – None reported.
NS – Not surveyed.

Table 11. Pharmacokinetic studies of selected saponins in rats, dogs or human plasma (after Lu et al 2009)[22]

Saponin	Species model, route	Dosage	Absolute bioavailability	Reference
25-OH-PPD	Rat, oral	10 mg/kg	64.8%	76
Rh2	Rat, oral	100 mg/kg	0.25%	154
Rh1, Rg1	Rat, i.v., or i.g.	100 mg/kg	1.33%	155
20(R)-, 20(S)-Rg2	Rat, i.v	25 mg/kg	-	156
Rd	Human plasma; in vitro	10 mg/kg	-	157
R1, Rg1, Rd, Re, Rb1	Rat, oral	10 mg/kg	9.29%, 6.06%, 2.36%, 7.06% and 1.18%	158,159
Rd	Dog, i.v., oral	2 mg/kg (oral) 0.2 mg/kg (i.v)	0.26%	160
Rg	Rat, oral	50 mg/kg	1.52%–6.60%	75
Rg3	Rat, oral	50 mg/kg	2.63	161,162
Multiple	Rat, oral	300 mg/kg	-	159
Rg1, Rb1	Rat, oral	50 mg/kg	18.4% (Rg1) 4.35% (Rb1)	163
Compound K	Rat, oral	20 mg/kg	35.0%	164

i.v.: intravenous administration; i.g.: intragastric gavage. - : no data/not tested.

Table 12. Pharmacokinetic parameters of saponins administered to rabbits.[85]

Saponin	Dose (Exposure route)	$t_{1/2}$ (min)	$t_{1/2}$ abs (min)	f (%)
Semi-purified A1	500mg in 10% ethanol (iv)	68.8	-	39
Semi-purified A1	500mg in 10% ethanol (iv)	79.9	-	68
Semi-purified A1	500mg in 10% ethanol (iv)	136	-	79
A1	500 mg in propylene glycol/ethanol/NaCl (ip)	25.3	9.90	39
A1	500 mg in propylene glycol/ethanol/NaCl (iv)	59.9	-	-
A1	250 mg in 10% ethanol (iv)	20.2	-	44
A1	500 mg in 10% ethanol (ip)	104	11.3	68
Semipurified A2	500 mg in 10% ethanol (ip)	24.7	363	61
Semipurified A2	500 mg in 10% ethanol (iv)	69.5	-	61
B2	500 mg in 10% ethanol (iv)	49.8	-	17
B2	500 mg in 10% ethanol (ip)	69.9	324	18
C	250 mg in 10% ethanol (iv)	478	-	41
C	500 mg in 10% ethanol (ip)	412	318	41

$t_{1/2}$ = elimination half life
$t_{1/2}$abs = absorption half life
f = fraction excreted unchanged in the urine

Table 13. Acute toxicity of various forms of ginseng.[165]

Compound	Species	Exposure route	LD_{50} (mg/kg)
Panax ginseng root	Rat	Oral	750
Panax ginseng root	Mouse	Oral	200
Panax ginseng root	Mouse	ip	54
Ginseng root extract	Mouse	ip	545
Saponin No. 3	Mouse	ip	910
Ginseng, saponin extract	Mouse	ip	637
Panabolide (TRIS-buffer extract of *P. ginseng*)	Rat	Oral	> 12,000
Panabolide (TRIS-buffer extract of *P. ginseng*)	Rat	ip	550
Panabolide (TRIS-buffer extract of *P. ginseng*)	Mouse	Oral	>2500
Panabolide (TRIS-buffer extract of *P. ginseng*)	Mouse	ip	>1050

Table 14. Reproductive and developmental studies of panax ginseng root extract (extracted with ethanol)**.**

Species (n)	Dose	Details	Results	Reference
White Wistar rats (10)	20 mg/kg	Days 6-15 of gestation by gavage	No signs of toxicity or behavior changes. No differences between controls and treatment group for embryo and fetal abnormalities.	166
Sprague-Dawley Rats (15)	0, 1.5, 5, 15 mg/kg/d in corn oil mixed in feed	Mated after 3 weeks treatment; females continued treatment through gestation; at weaning, F1 started on treatment feed and mated at 13 weeks; F2 raised to 21 days. All rats killed and necropsied.	F1 males and females had no treatment-related effects (i.e., body weight, feed consumption, hematology, clinical chemistry, ophthalmic, necropsy). Necropsy of F0 and F2 rats were unremarkable.	167

Table 15. Developmental studies of saponins**.**

Species	Dose	Details	Results	Reference
		Rb1		
Sprague-Dawley rats (27, 29, 25)	0, 5, 15, 30, 40, 50 µg/ml	9-day-old embryos were extracted from womb and cultured in equal volumes of rat serum and Dulbecco's modified Eagle's medium; penicillin; and streptomycin sulfate with Rb1. Embryos were examined after 48 h. Mean yolk sac diameter and crown-rump length were measured. Embryonic morphologies were given a numerical score (of 0-5) to 17 morphological features depending on their stage of development. Only viable embryos were included.	There were no morphological changes at 5 and 15 µg/ml. There were morphological changes to the flexon, forelimb, and hindlimb in the 30 µg/ml group with a lower total morphological score compared to controls. There were additional morphological changes to the heart and eye in the 40 µg/ml group. There was additional morphological changes to the CRL and somite number. There were no effects to the yolk sac diameter. Authors concluded that saponin Rb1 had a teratogenic effect on rat embryos.	168
ICR mice (20-21)	0, 5, 15, 30, 40, 50 µg/ml	Same as above	There were no morphological changes at 5 and 15 µg/ml except for yolk sac diamenter in the later. There were morphological changes to the yolk sac diameter and circulation, midbrain, forebrain optic system, and total score in the 30 and 40 µg/ml groups with a lower total morphological score compared to controls. There were additional morphological changes to the CRL, head length, somite number, allantosis, flexon, brachial arch, forelimb bud, and hindlimb bud in the 50 µg/ml group. There was additional morphological changes to the CRL and somite number. There were no effects to the yolk sac diameter. Authors concluded that saponin Rb1 had a teratogenic effect on rat embryos.	169
		Rc		
Rats (23-25)	0, 5, 50 µg/ml	Same as above	There were no differences in yolk sac diameter, CRL, number of somites, and total morphological score among control and embryos exposed to 5.0 and 50.0 µg/ml Rc	170
		Re		
Rats (23-25)	0, 5, 50 µg/ml	Same as above	Embryos exposed to 50.0 µg/ml Re had lower morphological scores for all parameters measured (see above) compared to controls. There was no difference between embryos exposed to Re and controls.	170

CRL – crown-rump length

Table 16. Reported effects in oral studies comparing ginseng and placebos (after Coon & Ernst 2002[66]).

Subject population	n treated	Preparation & daily dose	Duration	Reported effects		Reference
				Ginseng	Placebo	
Post-menopausal women	384	G115® 200mg	16wk	7 SAEs and 124 AEs Most frequent: flu/cold (36), headache (10), gastrointestinal (13)	9 SAEs and 133 AEs Most frequent: flu/cold (36), headache (10), gastrointestinal (13). Most frequent: flu/cold (35), headache (9), gastrointestinal (22)	[171]
Healthy men	36	G115® 200 and 400 mg	8 weeks	Diarrhea (3)	None reported	[172]
Healthy Volunteers	83	G115® 200mg	4 mo	Nausea (1)	Nausea, dizziness, headache, stomach problems (5)	[173]
Healthy Volunteers	227	G115® 200mg	12 weeks	Nausea, vomiting, anxiety, insomnia, epigastralgia (10)	Insomnia (1)	[174]
Healthy Volunteers	28	G115® 200mg	3 weeks	Diarrhea (2) – no treatment group specified		[175]
Patients with psycho-asthenic syndromes	60	G115® [dose not stated]	2 yr	Itching, eye burning (2)	Urticaria, itching, stomach pain, giddy feelings (4)	[176]
Patients with Hypertension	34	Red ginseng 4.5g root (300mg ginseng) ± other antihypertensive treatment	12wk	Upper abdominal discomfort (2) Also reported: diaphoresis, tiredness, constipation/dyspepsia (9) – no treatment group specified. Only 12 patients had ginseng alone	None reported	[177]
Healthy Volunteers	22	Korean ginseng 1000mg	30 d	Stimulation, improved motor efficiency, increased appetite, diarrhea, skin eruptions, sleeplessness, sleepiness (11)	Depression, improved motor efficiency, increased appetite sleeplessness (7)	[178]
Elderly patients	49	Korean red ginseng 1.5g	10 d	Diarrhea (1) – no treatment group specified		[179]
Women with postmenopausal osteoporosis	45	Red ginseng 50 mg/kg/d	12 mo	Digestion problem (3)	Digestion problem (1)	[180]
Patients with psychogenic impotence	35	Korean red ginseng 2700mg	2 mo	Digestive problem, diffuse itching (2)	None reported	[181]
Healthy Volunteers	64	Red ginseng/white ginseng 11.25g	10 d	Hyper- or hypothermia, hot flushes, diarrhea, headache, insomnia, constipation, lip dryness, dizziness, loss of appetite – no treatment group specified		[182]
Healthy radio operators	32	Liquid ginseng root extract 2ml	Single dose	Lighter hand and increased appetite (number of patients not reported)	None reported	[183]

G115® = standardized ginseng extract, 4% saponins (Ginsana®, Pharmaton SA, Lugano, Switzerland)
AE = adverse event
SAE = serious adverse event

Table 17. Placebo-controlled oral trials of ginseng in which no adverse effects were reported (after Coon & Ernst 2002[66]).

Subject population	n treated	Daily dose	Duration	Comments	Reference
Healthy females	19	G115® 200mg	8 wk	None	184
Healthy females	19	G115® 200mg	8 wk	None	185
Healthy males	16	G115® 200mg	12 wk	None	70
Patients with bronchitis	40	G115® 200mg	8 wk	Adverse effects not specified	186
Healthy subjects	112	400 mg Ginseng extract	8-9 wk	Six patients discontinued the study due to illness	187
Healthy males	41	Standard ginseng extract 300mg	8 wk	None	188
Patients with unsettled complaints	30	Korean red ginseng powder 2.7g	6 wk	None	189
Patients with erectile Dysfunction	90	Korean red ginseng 1800mg	3 mo	None	190
Athletes	30	Chinese ginseng 1200 mg	6 wk	None	191
Healthy nurses	12	Korean ginseng 1200 mg	3 d	None	192
Middle to old aged subjects	358	Panax ginseng 150 mg	2 mo	No vomiting and/or long-term toxic effects observed	192
Patients with diabetes mellitus	36	Ginseng 100 or 200 mg	8 wk	None	193

G115® = standardized ginseng extract, 4% saponins (Ginsana®, Pharmaton SA, Lugano, Switzerland)

Table 18. Effects reported in comparative oral trials comparing ginseng to another treatment (after Coon & Ernst 2002[66]).

Subject population	n treated	Daily dose	Duration	Effects reported (no. of patients)		Reference
				Ginseng	Other treatment(s)	
Patients with chronic bronchitis	75	G115® 200mg/ antibacterial Treatment	9 d	Not specified; Nine patients withdrew from the study spontaneously (no treatment group specified)	Not specified	194
Sportsmen	20	G115® 200mg/G115s	9 wk	None reported	None reported	195
Patients with heart failure	45	Red ginseng [dose not stated]/ digoxin/both	15 pills	None reported	None reported	196
Regular users of ginseng	18	Self-regulated doses of *P. ginseng* capsules (~518-1300 µg/d), teas (1-2 cups), extracts (2.5-5.0 ml), or root (0.5-3.0 g/d) with and without other stimulants	12 wk	Ginseng - Contact urticarial reaction (1), stimulation, feeling of wellbeing, nervousness	Ginseng and other stimulants - allergic reactions (2), ginseng abuse syndrome (1), stimulation, wellbeing	197

G115® = standardized ginseng extract, 4% saponins (Ginsana®, Pharmaton SA, Lugano, Switzerland); **G115s** = standardized ginseng extract, 7% saponins (Pharmaton SA, Lugano, Switzerland); **n** = number of study participants.

Table 19. Effects reported in uncontrolled trials of ginseng (after Coon & Ernst 2002[66]).

Subject population	n	Daily dose	Duration	Adverse effects reported (no. of patients)	Reference
Patients with oligospermia	17	G115® 400mg	90 d	None reported	198
Patients with chronic respiratory disease	15	G115® 400mg	3 mo	None reported	199
Postmenopausal women	49	G115® 200mg	3 mo	None reported	200
Postmenopausal women with and without climacteric symptoms	20	Korean red ginseng 6 g	30 d	None reported	201
Male athletes	10	Pure ginseng extract 105 mg	2 d	None reported	202
Patients with essential hypertension	35	Ginseng extract 1000 mg	Up to 10 wk	None reported	203
Healthy women	20	Epicutaneous extract of ginseng containing 14% gensenosides	30 d	Patients withdrew after 12-15 days due to skin feeling "too tight" (3)	204
Patients with essential hypertension	19	Red ginseng powder 3 g	12 wk	None reported	205
Patients with hypertension	17	Korean red ginseng 4.5 g	21-27 mo	None reported	206
Patients with mild proteinaemia and hypertension	24	Red ginseng 900 mg	2 mo	Digestive problem (1)	207

G115® = standardized ginseng extract, 4% saponins (Ginsana®, Pharmaton SA, Lugano, Switzerland);

Table 20. Summaries of reports/studies on the estrogenic activity of products containing ginseng and ginseng saponins, and various ginseng extracts and saponins.

Ginseng source/description	Report/study summary	Reference
	Human – Anecdotal reports	
Fang Fang ginseng face cream (no information was found on the contents of the cream)	A 44-yr-old woman who had undergone menopause at age 42 experienced three episodes of vaginal spotting after daily use of Fang Fang ginseng face cream for 1 month or more (Shanghai, China; formula unspecified). The bleeding episodes were associated with a decrease in follicle-stimulating hormone (FSH) levels and a disordered proliferative pattern on endometrial biopsy. The woman experienced no further bleeding after discontinuing use of the cream.	122
P. ginseng; 200 mg/tablet (formula and duration not provided)	A 72-year-old woman experienced vaginal bleeding after ingesting one tablet daily of a Swiss-Austrian geriatric formula containing *P. ginseng*.	121
P. ginseng powder (formula, dose, and exposure route not provided)	A 70-year-old woman developed mastalgia with diffuse nodularity after using a *P. ginseng* powder for 3 weeks. The symptoms ceased after the use of the product was discontinued, and reappeared with two additional re-challenges. Prolactin levels remained within normal limits.	124
"Rumanian" ginseng (form and amount not provided)	A 62-year old woman who had undergone bilateral oophorectomy 14 years previously developed marked estrogenic effects, based on the microscopy of vaginal smears and gross appearance of the vaginal and cervical epithelium, after ingesting Rumanian ginseng two weeks per month for 1 year. Estrone, estradiol, and estriol levels were essentially unchanged over this time, but the effects on the vaginal smear coincided with the use of the product. The investigators found no estrogen in the product. However, a crude methanol extract of the product competed with estradiol for binding to estrogen and progesterone receptors in human myometrial cytosol.	126
Ginseng preparations (species, formula, amount and exposure route and durations not provided)	Five women aged 25-40 who had been taking ginseng preparations developed breast symptoms, including enlargement of the nipples.	123
Ginseng (species, formula, amount and exposure route and duration not	Male gynecomastia has also been reported after ginseng use.	125

Table 20. Summaries of reports/studies on the estrogenic activity of products containing ginseng and ginseng saponins, and various ginseng extracts and saponins.

Ginseng source/description	Report/study summary	Reference
provided)		
	Whole Animal Studies	
P. ginseng (ethanol extracts; 2 weeks at 0, 125, 250, 500, 1000, or 2000 mg/kg 5 days/week; 3 months at 0, 1000, 2000, 3000, 4000, or 5000 mg/kg, five days per week))	Oral toxicity and carcinogenicity studies of ethanol extracts of *P. ginseng* in Fischer 344 rats and B6C3F1mice studies, there were no significant differences in sperm parameters of male rats and mice or the estrous cyclicity of female rats and mice between the control and ginseng treated groups. No evidence of hormonal effects in rats or mice was found in these studies, including the two-year study (0, 1250, 2500, 5000 mg/kg five days per week).	130
P. quinquefolium (purchased from a health-food vendor)	Alcohol extracts of *P. quinquefolium* had no effect on uterine weight when administered by gavage (500 µl/day) to ovariectomized CD-1 mice for 4 days. In contrast, 100 µg/kg/day 17β-estradiol administered subcutaneously for 4 days increased the mean uterine weight 1.7-fold greater than the negative control group.	129
	In vitro studies	
P. quinquefolium "high" concentrations (ie, 1:500 dilution)	Alcohol extracts of *P. quinquefolium* stimulated the growth of MCF-7 cells, which are estrogen receptor (ER)-positive human breast cancer cells. The proliferation rate of the treated cells was 2 times greater than that of untreated control cells, but the treatment did not transactivate (ie, did not increase the rate of gene expression of) either human ERα (hERα) or hERβ in transfected HeLa cells. The authors suggested that ginseng stimulates the growth of MCF-7 cells independent of estrogenic activity.	129
P. quinquefolium (multi-solvent extraction and a proprietary extract)	*P. quinquefolium* extracts induced the expression of the estrogen-sensitive gene, pS2, and caused a dose-dependent decrease in the proliferation of MCF-7 cells.	134,135
P. quinquefolium root (various extract solvents)	Extraction method of *P. quinquefolium* root determined its ability to produce an estrogenic response in MCF-7 cells. A methanol extract, but not a water extract, increased MCF-7 cell proliferation in a concentration-dependent manner at low concentrations (5-100 µg/ml) when the cells were maintained under low-estrogen conditions. Higher concentrations of the methanol extract inhibited proliferation. The results of proliferation studies, ER binding assays, and pS2 and progesterone receptor (PgR) mRNA expression analyses all supported the conclusion that the water extract does not elicit estrogen-like activity. The authors proposed that the conflicting results of laboratory studies on the estrogenicity of ginseng may be attributable to differences in extraction methods.	138
P. ginseng and *P. quinquefolius* root	Crude water or methanol extracts of *P. ginseng* and *P. quinquefolius* root can bind to purified ERα or ERβ (PanVera), but neither receptor type interacted with purified Rb1 or Rg1 (Indofine). However, the crude extracts contained zearalenone or zearalenone-like compounds that bind to ERα and ERβ, and three of the four root samples cultured positive for Fusarium fungus, which is the only known natural source of zearalenone. Zearalenone and its metabolites are well-known, potent estrogenic mycotoxins. The authors suggested that the findings could explain the sporadic reports of estrogen toxicity after ginseng use, as well as the conflicting results of in vitro studies of the estrogenic action of ginseng crude extracts and purified ginsenosides.	137
Rb1	50 µM Rb1 obtained from the Korean Ginseng and Tobacco Research Institute (purity unspecified), activated the transcription of the estrogen-responsive luciferase reporter gene in MCF-7 cells. The effect was blocked by the specific ER antagonist ICI 182,780, indicating that the effect is ER-dependent. The authors proposed that Rb1 acts as a weak phytoestrogen, presumably by binding and activating the estrogen receptor in these cells.	143
Rb1 from the Korean Ginseng and Tobacco Research Institute (purity unspecified)	Rb1 activated both ERα and ERβ, leading to the transactivation of estrogen-responsive luciferase genes in MCF-7 cells in a dose-dependent manner (up to 100 µM). However, Rb1 did not displace the specific binding of [^{3}H]17β-estradiol from estrogen receptors in MCF-7 whole-cell ligand binding assays. Thus, Rb1 appears to activate both ERα and ERβ in these cells in the absence of ER binding.	133
Rb1 purchased from the National Institute for the Control of Pharmaceutical and Biological Products	Rb1 (>98% purity, 0 and 500 nM for 24 hours) activated the anti-angiogenic pigment epithelium-derived factor (PEDF), and suppressed endothelial cell tube formation, in human umbilical vein endothelial cells (HUVEC). These effects were mediated by ERβ, rather than ERα. In competitive ligand binding assays, Rb1 was able to displace a high-affinity fluorescent estrogen ligand from human recombinant ERβ, but not ERα.	144
Rc and Re	Rc and Re can stimulate MCF-7 cell growth and induce c-Fos expression independent of ER activation.	142
Re	Re did not enhance proliferation of MCF-7 cells.	136
Rg1 from the ethanol extracts of *P. notoginseng*	Picomolar (pM) concentrations of 99% pure Rg1 from the ethanol extracts of *P. notoginseng* can activate the ER in human breast cancer cells (MCF-7) and human endometrial cells (HeLa) without directly interacting with the ER.	131
Rg1	Rg1 stimulated MCF-7 cell proliferation and pS2 mRNA expression through activation of cross-talk between ERα-dependent and insulin growth factor 1 receptor (IGF-IR)-dependent pathways.	132

Table 20. Summaries of reports/studies on the estrogenic activity of products containing ginseng and ginseng saponins, and various ginseng extracts and saponins.

Ginseng source/description	Report/study summary	Reference
Rg1	Rg1 stimulates the transcription of the estrogen response element (ERE)-luciferase reporter gene through ERα and ERβ in human embryonic kidney cells (HEK293) transfected with either ERα or ERβ. However, Rg1 activated ERE-luciferase activity at lower concentrations (0.01 pM to 1 μM) through the ERα-mediated pathway, compared to the Rg1 concentration (1 μM) required for activation through the ERβ-mediated pathway. Furthermore, 1 pM Rg1 rapidly induced the phosphorylation at the serine 118 residue of the AF-1 transcriptional activation domain of ERα within 5 minutes, suggesting that Rg1 activates ERα in a ligand-independent manner. The authors suggested that the results may help to explain the different effects of ginsenosides in different types of tissues.	140
Rg1	The estrogenic effects of Rg1 (>99% pure) in MCF-7 cells, including the ligand-independent activation of ERα, the induction of IGF-IR and estrogen-responsive pS2 expression, and the stimulation of cell proliferation, are mediated by the mitogen-activated protein kinase (MAPK) pathway.	141
Rh1	Rh1 (50 μM) could activate ER in human breast cancer cells.	143
Rh2 (semi-synthesized; 10^{-7}-10^{-6} M)	Estrogenic potency of semi-synthesized ginsenoside-Rh2, was examined with yeast two-hybrid system, including expressed genes of human estrogen receptor, hERα, the co-activator TIF2 and lacZ as a reporter gene. Ginsenoside-Rh2 exhibited moderate estrogenic activity at 10−7 to 10−6 M. Its effect was approximately 30% of the activity of 17β-estradiol applied at half-effective concentration. The authors concluded that this indicatesd that Rh2 is a weak phytoestrogen. Data obtained by yeast two-hybrid assay reflect structure–activity relationship between tested compounds and 17β-estradiol. Rh2 has some similarity in chemical structure with 17β-estradiol that might explain affinity of this glycoside to the hERα receptor.	139

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Data

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: July 12, 2012

SUBJECT: Comments on the Tentative Report on the Panax Root-Derived Ingredients

Key Issues

For each study, the type of extract used, e.g., extracted in ethanol, should be stated. Specific studies for which this information needs to be added are provided below.

The limit for pulegone in finished products is stated as ≤1% in the Abstract, and as 0.03% for rinse-off products and 0.002% for leave-on products in the Discussion. The basis of the limit on pulegone comes from the peppermint report which had a limit of ≤1% in ingredients not finished products. Therefore, the value in the Abstract is not correct, and it should be revised to be consistent with the Discussion.

Additional Comments

Cover - Although the Tentative report is dated June 12, 2012, this report was not posted on the CIR website until July 2, 2012. The date on the report should be the date the report was posted. The cover of Tentative Reports should indicate that there is a 60 day comment period for this report. At the June 11-12, 2012 meeting, the CIR Expert Panel requested that "On the" should be deleted from the title of the report.

p.1 - As the Agricultural Research Services GRIN database shows that there are 48 Panax species, it would be more appropriate to state that there are "several species within the genus" (4) used in cosmetics, rather than stating that there are "many species".

p.1, 2 - Please correct the spelling of "japonic[a]s"

p.4, Cosmetic Use Section - It would be helpful if the text of the Cosmetic Use section provided some information in addition to that found in Table 10, such as the specific FDA product categories with the highest use concentration and specific FDA product categories with the most reported uses. A discussion concerning the use of these ingredients in potential spray products still needs to be added to this section.

p.4 - In which species was the bioavailability of 25-OH-protopanaxadiol 64.8 ± 14.3%?

p.4 - The meaning of the following is not clear "and its hydrated form under acid conditions similar to gastric fluid."

p.4 - In reference 77, were mice really dosed orally with M1? Or is M1 just a metabolite of Rb1? If mice were actually dosed with M1, the results of the M1 dosing study should also be stated.
p.5 - Please indicate the type of *P. ginseng* root extract used to treat the B6C3F1 mice (reference 84). The Repeated Dose Exposure section could also be re-written to present all the NTP studies together so that it could be stated once that in all of the NTP studies, an 80% aqueous ethanol extract was used.
p.6 - Please indicate that reference 86 is a review.
p.6 - What type of extract was used in reference 87?
p.6 - What type of extract was used in reference 88?
p.6 - What type of extract was used in reference 91?
p.6 - What type of extract was used in reference 12?
p.6 - What type of extract was used in reference 95?
p.7 - Both TNCB and oxazolone are sensitizers. The studies in the Dermal-Nonhuman subsection under the Irritation heading, appear to be assessing the ability of *Panax ginseng*-derived ingredients to decrease the symptoms of sensitization. The subsection heading needs to be revised.
p.7 - What type of extract was used in reference 103?
p.7 - What type of extract was used in reference 82?
p.7-8 - What type of extract was used in reference 14?
p.8 - What type of extract was used in reference 112?
p.9 - In the first paragraph, please add "root" to "panax ginseng water"
p.9 - The negative NTP carcinogenicity studies should be added to the Summary.
p.9 - In the Summary, please provide the dose that is associated with adverse effects in humans.
p.9 - As the potential phytoestrogenic activity is already discussed, the second last paragraph of the Summary should be deleted.
p13, Table 2 in the Value column under Panax Ginseng Root Powder, please correct the spelling of "wite"
p.15-24, Table 4 and Table 5 - Please sort the table by "Part".
p.25, Table 6 and Table 7 - As only one part is in each table, the Part column is not needed and the part should be stated in the title of the table. As there is nothing in the Lo (ppm) column of either table, this column should be deleted from both Table 6 and Table 7.
p.26, Table 8 - Please indicate how the ingredients in this table were extracted.
p.26, Table 9 - Please add the species that was used as the source of the extracts in Table 9.
p.26, Table 10 - The 0.1% concentration in the Incidental Inhalation-sprays row under Panax Ginseng Root Extract should have a footnote to indicate that it is not known whether or not this product is a spray.
p.26, Table 10 - The 0.0005% concentration in the Hair-noncoloring row under Panax Quinquefolium Root Extract is a shampoo. According to the table on the CIR website http://www.cir-safety.org/sites/default/files/imports/usemethod.pdf, shampoos should not be included in the Mucous Membrane row. Therefore, the 0.0005% concentration needs to be deleted from the Mucous Membrane row.
p.27, Table 11 - Please indicate what "-" means in this table. What was the route of exposure for humans in reference 151? In the row for reference 152, 153 there are four compounds listed in

the Saponin column, but five values listed in the Absolute bioavailability column. It is not clear what the five values in the Absolute bioavailability column represent. "In vivo" in the species model, route column for reference 69 can be deleted, as the oral exposure route would require a live animal experiment.

p.28, Table 14 - Please indicate the type of extract used in the studies summarized in this table.

p.30-31, Tables 16, 17 and 18 - In these tables, it is not clear what n represents. Is n the total number of subjects, or the number of subjects treated with ginseng? It is not clear if some of the subjects in the studies with placebos served as their own controls.

p.31, Table 18 - What was the dose used in reference 191? It is not clear how "wellbeing" represents an effect reported by patients.

p.32, Table 20 - As "Rumanian"ginseng is the wrong species, please delete reference 120 from this table.

p.34, Table 20 - Please revise the Results/study summary column for reference 137. It currently states: "Rh1 could activate ER in human breast cancer cells." Please indicate the lowest concentration of Rh1 that activated human breast cancer cells, or the highest concentration of Rh1 that did not have any effects.