American Ginseng – Panax quinquefolius L.

1. Taxonomy

*Panax quinquefolius* L.
Family: Araliaceae
Common names: American ginseng, five finger root, sang, tartar root, redberry, man’s health, root of life, dwarf groundnut, garantogen, jinshard, ninsin, little man, garent-oquen.

Two species of *Panax* (*P. quinquefolius* and *P. trifolius* L.) are native to North America. The latter species is much smaller and rarely used for medicinal purposes. There are 11 species globally, several of which are Asian, most notably *P. ginseng* C.A.Mey. known as Korean or Asian ginseng.

2. Botany and distribution

*P. quinquefolius* is a slender deciduous perennial growing to a height of 2 feet and bearing palmate-compound, serrated leaves at the apex of the stem. Individual leaflets range from lance
shape to oblong. Leaves from young plants may consist of only three leaflets. As the plant matures, more sets of these leaves appear, but it is rare to see plants with four or more compound leaves or ‘prongs’ as they are known. As the stem (‘sympodium’) dies back each fall it leaves a bud scar on the root collar or rhizome - these are used as a means of assessing the plant’s age (Rural Action Inc., 2005). Adventitious roots may form from these nodes in older plants (Van Der Voort, Bailey, Samuel, & McGraw, 2003).

Small whitish flowers appear in the summer, born on a simple umbel in the main leaf axis. These are followed by red berry-like fruit containing up to three seeds. Seeds remain dormant for well over a year, germinating in the second spring season (Schlag & McIntosh, 2004). *P. quinquefolius* also has the ability to remain in a dormant state for a year or several years when weather conditions are adverse (Taylor, 2006).

Ginseng roots are fleshy white or light colored tap roots, and variably branched. As the plant ages it sometimes puts out an auxiliary root that may act as a ‘spare’ if the main root is damaged (Elliot, 1976)

The preferred habitat for *P. quinquefolius* is in the shady understory of deciduous hardwood forests in Eastern USA and Canada. It was once quite prevalent in the Appalachian region though now its distribution is quite patchy (Case, Flinn, Jancaitis, Alley, & Paxton, 2007; McGraw, Sanders, & Voort, 2003) and gene flow between populations is restricted (Assinewe, Baum, Gagnon, & Arnason, 2003; Cruse-Sanders & Hamrick, 2004). It likes well-drained, humus-rich soil and prefers east-facing slopes (Foster & Johnson, 2006).

**Parts Used**
The dried root, harvested from plants at least 6 years old, in late summer and fall. Research indicates the leaves and fruit are also pharmacologically active.

### 3. Traditional Uses

**Traditional use in Appalachia**

*P. quinquefolius* has traditionally been administered as a tea for general tonic purposes and as an aphrodisiac. It is used to dispel a cough and promote perspiration in colds, driving out the force of illness from within (Crellin & Philpott, 1990). It is cultivated and revered in central and eastern North America by tribal and Appalachian cultures for its longevity-promoting effects, although differentiation between Chinese and American ginseng uses has often been blurred (Duke, 1986; Millspaugh, 1974). *P. quinquefolius* has also been used as a poultice for boils and decoctions of the roots have been taken to relieve headaches and “female troubles” (Banks, 2004). It is said that the root of *P. quinquefolius* ceased unpleasant dreams in children and infants and remedied issues relating to flatulence and colic (Howell, 2006).

*P. quinquefolius* has been traded interstate and overseas for hundreds of years, and it remains an integral part of the Appalachian economy (Cavender, 2003).

**Traditional use - general**

European interest in *P. quinquefolius* can be dated back to the early 18th century when a French Jesuit, Joseph-Francois Lafitau, spent many years amongst the Canadian Mohawk Nation
searching for an American equivalent to Asian ginseng. His quest was so successful that a ginseng industry was quickly established, and within a few years large quantities were being exported to China (Taylor, 2006).

**Native American**
Before Lafitau’s discovery of the similarity between Asian and American ginseng, *P. quinquefolius* was already a medicinal agent in native traditions (Taylor, 2006). The Iroquois Indians used ginseng for a variety of disorders including upset stomach, sore eyes and tape worm, but also as an article “to give thanks and for preventative health care” (Taylor, 2006). Other recorded Native American uses of this herb included applications as an analgesic, anticonvulsive, expectorant, digestive tonic, gynecological aid, & general tonic (Moerman, 1998). It was sometimes used as a remedy for headaches and colic.

**Folklore & Home**
The main home use of American ginseng was as a digestive stimulant particularly for the weakened or uneasy stomach. It was also used to treat a sluggish nervous system and strengthen the circulation (Harding, 1936).

**Physiomedical**
*P. quinquefolius* was said to have sedating and relaxing effects, and was used to address dyspepsia as well as nervous sensitiveness with debility (Cook, 1869). Its main action was a nerve tonic and relaxant to the whole body, with a particular affinity for the brain.

**Eclectic**
Felter (1922) and Scudder (1870) report that the root of *P. quinquefolius* required long-term use to be effective. It was used as a nervous system sedative, having the greatest effects on calming nervous dyspepsia as well as “mental and other forms of nervous exhaustion from overwork.” Felter noted its use as a long term, building tonic for patients with depleted resources, particularly cerebral anemia (Felter, 1898).

**Regulars**
Allopathic physicians found little use for *P. quinquefolius* except as a demulcent and as a flavorful root to chew (Remington & Wood, 1918). Many believed that ginseng’s medicinal qualities were a myth of the Chinese and had little use for it in this country as an effective medicine (Wood & Bache, 1858). Nevertheless *P. quinquefolius* was official in the United States Pharmacopoeia (USP) from 1842 until 1882 (Blumenthal, 2003).

**China**
*P. quinquefolius* is used in Traditional Chinese Medicine to treat “deficiency” conditions associated with symptoms such as fatigue, irritability, thirst and dryness of the mouth or respiratory tract (Chen & Chen, 2004).

### 4. Scientific Research

**Phytochemistry**
The most significant group of active constituents in *P quinquefolius* and *P. ginseng* are a group of triterpenoid saponins known as ginsenosides. Ginsenosides are glycosides whose aglycones have dammarane-type structures. A rare ocotillo-type saponin known as 24-R-
pseudoginsenoside is found only in P. quinquefolius (Leung & Wong, 2010). Another class of
dammarane-type triperpene oligoglycosides (quinquenosides I-V) are also found in the species
(Yoshikawa et al., 1998).

A wide range of extraction, separation and detection methods have been applied for the
determination of ginsenoside structures and levels in different plant sections. These methods
include high-performance liquid chromatography (HPLC), mass spectroscopy (MS), diode-array
detectors (DAD), infra-red (IR) spectroscopy and evaporative light scattering detection (ELSD)
(Ferreira, Ebbs, Murphy, & Corbit, 2005; Jia, Zhao, & Liang, 2009; Orsat & Dai, 2010; Qi,
Wang, & Yuan, 2011; Wan, Li, Chen, & Wang, 2007; Yat et al., 1998). The United States
Monograph (USP, 2004) includes TLC and HPLC methods for ginsenoside evaluation, with the
acceptable total content being no less than 4% of the dried roots (USP, 2004). Modifications to
the USP methods have been recommended, in an attempt to overcome inconsistent results
observed from the use of different HPLC columns (Li, Chen, Chou, Want, & Hu, 2004). For
identity of pseudoginsenoside F11, HPLC was coupled with ELSD (Li & Fitzloff, 2001).

further analyzed five ginseng species by principal component analysis and found that P.
quinquefolius was readily discriminated from the other four species tested.
Gene sequencing experiments have also led to an understanding of the biosynthesis of
ginsenosides; the genes encoding enzymes identified include 150 cytochrome P450 and 235
glycosyltransferase sequences unique to P. quinquefolius (Sun et al., 2010).

Ginsenosides are classified into two main groups known as protopanaxadiol (PPD) and
protopanaxatriol (PPT), based on the hydroxylation pattern at C6 and attachment of sugar
moieties (Table 1). Phytochemically Panax species are distinguished by the ratio between these
groups (Hall, Lu, Yat, Fitzloff, et al. 2001). For example P. ginseng ginsenosides are mainly of
the PPD group, while PPTs are more prominent in P. quinquefolius although Rf is entirely
absent. Further differentiation may be made by the ratios of Rg1/Rb1 and Rb2/Rb1 which tend to
be higher in P. ginseng (Yuan, Wang, Wicks, & Qi, 2010) although some wild populations of P.
quinquefolius have been found to have high Rg1/Rb1 ratios (Schlag & McIntosh, 2006). As a
generalization the most prominent P. quinquefolius constituents are Rb1 and Re (Assinewe et al.,
2003). However North America P. quinquefolius populations have been further differentiated
according to their Rg1/Re ratio (Schlag & McIntosh, 2006; McIntyre et al. 2011). The variation
in chemotypes is not only significant for identification purposes - they also have clinical
implications as discussed below under metabolism. The main ginsenosides in P. quinquefolius
are listed in Table 2.
Table 1. Classification of ginsenosides in *Panax* spp. (Leung & Wong, 2010). Compounds are named according to a decreasing polarity scale (i.e. water solubility). Generally the PPT group is more polar due to the extra hydroxyl group e.g. Re, while the less polar PPDs tend to be lower in the alphabet e.g. Rb.

<table>
<thead>
<tr>
<th>Protopanaxadiol group (PPD)</th>
<th>Protopanaxatriol group (PPT)</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rb1, Rb2, Rb3</td>
<td>Re</td>
<td>F11 ocotillo saponin (<em>P. quinquefolius</em> only)</td>
</tr>
<tr>
<td>Rc</td>
<td>Rf (<em>P. ginseng</em> only)</td>
<td>Oleanane saponins</td>
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<tr>
<td>Rd</td>
<td>Rg1, Rg2</td>
<td>Quinquenosides</td>
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<tr>
<td>Rg3</td>
<td>Rh1</td>
<td></td>
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<tr>
<td>Rh2</td>
<td></td>
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<tr>
<td>Rs1</td>
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Table 2: Main ginsenosides and ratios typical of *P. quinquefolius*

<table>
<thead>
<tr>
<th>Ginsenosides and their ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rb1</td>
</tr>
<tr>
<td>Rg1</td>
</tr>
<tr>
<td>Rg1 / Rb1 &lt; 1 (see text for clarification)</td>
</tr>
<tr>
<td>Re</td>
</tr>
<tr>
<td>F11 ocotillo saponin - 24R-pseudoginsenoside</td>
</tr>
<tr>
<td>Rf / F11 ratio =0.1</td>
</tr>
</tbody>
</table>

Ginsenoside content will also vary as a consequence of increased temperatures. *P. quinquefolius* grown at high temperatures tends to accumulate less biomass and develop smaller roots, leading to a reduction in total ginsenoside content (though not concentration) in plants subjected to a 5°C increase in growth temperatures in comparison to controls (Jochum, Mudge, & Thomas, 2007). Preferential selection of larger roots for analysis of ginsenosides and polyacetylenes did not influence the concentrations of either group of constituents (Christensen & Jensen, 2008). Ginsenoside levels are not influenced by root shape or section harvested, although root “fibre”
has higher concentrations - though not of Rb1 (Roy, Grohs, & Reeleder, 2003). Other factors that may act as predictors of ginsenoside concentration are age and stage of plant development, soil pH, light concentration (Schlag, 2004) and understory light levels including the effect of sun flecks (Fourniera et al, 2003), while variation may also be found between cultivated, wild and wild-simulated plant material – this in turn is influenced by the seed source (Schlag, 2004). Exposure of the roots to soil-borne heavy metals such as lead and arsenic can also influence ginsenoside production in ginseng roots (Corbit, Ebbs, King, & Murphy, 2006).

In a surprise finding, J.-T. Xie et al (2004) revealed that for Wisconsin cultivated P. quinquefolius the leaves contain far higher levels of ginsenosides (15.3%) compared to the berries (10.8%) and root (5.5%), and the ratio of the leaf components also differed, with particularly high concentrations of Rd and Re. By contrast Assinewe et al (2003) found the leaves of seven wild populations to contain only 3.33% ginsenosides compared with 5.78% for root.

Huge variability exists between different ginseng commercial products, partly due the number of species marketed as ginseng, as well as differences within products from the same species (Harkey, Henderson, Gershwin, Stern, & Hackman, 2001). In an attempt to identify mislabeled and adulterated products marketed as ginseng in North America, and to develop a set of standardized tests for identity and quality, the American Botanical Council initiated the Ginseng Evaluation Program in collaboration with the Universities of Ottawa and Chicago (Hall, Lu, Fitzloff, Arnason, Awang, Fong, & Blumenthal, 2001).

**Pharmacokinetics**

There have been few pharmacokinetic investigations into P. quinquefolius. Those available are based around the ginsenosides, which are found to be of low bioavailability (Jia et al., 2009; Reeds et al., 2011). This is partly a result of the first-pass metabolism that occurs, leading to formation of metabolites which may in fact be more potent that the ginsenoside ‘pro-drugs’ from which they derive (Bae et al., 2004).

Ginseng saponins appear to be readily degraded under mild acid conditions such as found in the human stomach. For example ginsenosides Rg1, Re and Rb1 were shown to yield their prosapogenins under such conditions (Han et al., 1982). In further studies Bae, Han, Choo, Park, and Kim (2002) demonstrated the formation of ginsenoside Rg3 following mild acid treatment. This Rg3 metabolite was further transformed by human intestinal bacteria to Rh2, which showed increased cytotoxicity against tumor cells and *Heliobacter pylori* *in vitro*. Ginsenoside Rb1 occurs in both an acid form (malonyl-Rb1) and the neutral form, which in cultivated *P. quinquefolius* are in approximately equal proportions (Awang, 2000). The acidic form can be converted to neutral Rb1 by steaming or by digestion in the stomach, after which it is further converted by anaerobic bacterial enzymes to a more polar and more active metabolite - Rd (Kim, Lee, & Lee, 2005). Removal of glucose units from Rd by intestinal bacteria leads to formation of Intestinal Bacterial Metabolite (IBM) also called compound K – this unit can be absorbed into the bloodstream (Awang, 2000). Ginsenosides Rb2, Rc and Rd follow a similar route.

Ginseng metabolites have also been shown to have more significant cytochrome P450 influence compared to the natural saponins (Liu et al., 2006). These studies provide further evidence that ginsenosides actually act as pro-drugs, which depend on transformation by stomach acid and
intestinal bacteria to release their active constituents (Bae, Han, Kim, & Kim, 2004). For a flow chart that displays the stages of biotransformation of the various ginsenosides by intestinal microflora to their metabolites, see Leung & Wong (2010).

In addition to first pass effect, ginsenoside profiles may also be influenced by steaming ginseng—a common tradition in Asia. HPLC profile comparisons between steamed and unsteamed *P. quinquefolius* roots have been published (Qi, Wang, & Yuan, 2010). When berries were steamed in a separate study, the overall level of ginsenosides was reduced however there was significant augmentation of Rg3, a recognized anticancer agent (Wang et al., 2006). Rg3 has also been identified in heat-processed *P. ginseng* (Bae, et al. 2002).

**Polyacetylenes**
Polyacetylenes are small lipid soluble molecules of limited distribution in plants. The major such compounds in *P. quinquefolius* roots are the alcohols falcarniol and panaxydol (Christensen, Jensen, & Kidmose, 2006), while others include PQ-1→PQ-8 (all previously unknown), panaxytyrol, acetylpanaxydol and ginsenoyne G (Fujimoto, Satoh, Takeuchi, & Kirisawa, 1991; Fujimoto, Wang, Kirisawa, Satoh, & Takeuchi, 1992; Fujimoto, Wang, Satoh, & Takeuchi, 1994; Satoh et al., 2007) and a recently discovered compound 3-oxy-PQ-1 (Satoh et al., 2007). The main analytical methods for identification and quantification of polyacetylenes in *P. quinquefolius* roots are HPLC, MS and C/H-NMR, while Christensen et al. (2006) have developed an HPLC method for simultaneous analysis of ginsenosides and polyacetylenes.

**Polysaccharides**
Numerous polysaccharides as well as oligosaccharides and monosaccharides have been extracted from *P. quinquefolius*. Assinewe, Amason, Aubry, Mullin, & Lemaire (2002) extracted a linear polysaccharide fraction which, upon acid hydrolysis, was found to yield mainly glucose with small amounts of galactose and arabinose and a 9% uronic residue. A commercial extract standardized to polysaccharide content has been developed by CT Technologies. CVT-E002 (COLD-fx®) is comprised of poly-furanosyl-pyranosyl-saccharides that have been shown to stimulate the immune system (Shan, Rodgers, Lai, & Sutherland, 2007).

**Other constituents**
Apart from saponins *P. quinquefolius* contains phenolic compounds, amino acids, flavonoids, volatile oils, vitamins and minerals (Schlag, 2004; Jia et al, 2009; Qi, Wang, & Yuan, 2011).

**Pharmacology**

**Pharmacology of ginsenosides**
As mentioned above, individual ginsenosides provide significantly different pharmacological effects, hence the interest in ascertaining specific levels and ratios. This is exemplified by the two major ginsenosides – Rb1 and Rg1 – characteristic of *P. quinquefolius* and *P. ginseng* respectively. Rb1 tends to be more of a depressant (more “yin”, eg inhibiting angiogenesis) while Rg1 is a mild stimulant (more “yang”, eg. promoting angiogenesis) (Harkey et al., 2001; Sengupta et al., 2004). Further correlations between individual ginsenosides and their activities are listed in Table 3.
### Table 3. Some pharmacological effects of ginsenosides

<table>
<thead>
<tr>
<th>Compound</th>
<th>Pharmacological action</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Rb1</td>
<td>Estrogen-like activity</td>
<td>Benishin, Lee, Wang, &amp; Liu, 1991; Duda et al., 1996; Papapetropoulos, 2007; Radad et al., 2004; Rudakewich, Ba, &amp; Benishin, 2001; Sengupta et al., 2004; Shang et al., 2007; Shang et al. 2008; Xiong et al., 2010</td>
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<tr>
<td></td>
<td>Anti-diabetic, insulin sensitizing</td>
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<td></td>
<td>Antiobesity</td>
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<td></td>
<td>Angiogenesis inhibitor</td>
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<td></td>
<td>Neurotropic, neuroprotective</td>
<td></td>
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<tr>
<td>Rc</td>
<td>Inhibit proliferation of breast cancer cells</td>
<td>Murphy, 2002</td>
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<tr>
<td>Re</td>
<td>Anti-diabetic</td>
<td>Attele et al., 2002; Yuan et al., 2010</td>
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<tr>
<td></td>
<td>Antioxidant, cardioprotective</td>
<td></td>
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<tr>
<td>Rg1</td>
<td>Neurotropic, neuroprotective</td>
<td>Chen, Chen, Zhu, Fang, &amp; Chen, 2002; Chen et al., 2003; Lee et al., 1997; Radad et al., 2004; Rudakewich et al., 2001; Radad et al., 2004; Sengupta et al., 2004</td>
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<tr>
<td></td>
<td>Ligand for glucocorticoid receptor</td>
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<tr>
<td></td>
<td>Suppresses oxidative stress</td>
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</tr>
<tr>
<td></td>
<td>Promotes angiogenesis</td>
<td></td>
</tr>
<tr>
<td>Rg2</td>
<td>Neuronal Ach inhibitor</td>
<td>Sala et al., 2002</td>
</tr>
<tr>
<td>Rg3</td>
<td>Inhibits proliferation of prostate cancer cells</td>
<td>H-S Kim et al., 2004</td>
</tr>
<tr>
<td>Rh1</td>
<td>Activates estrogen receptor</td>
<td>Lee et al., 2003</td>
</tr>
<tr>
<td>Rh2</td>
<td>Cytotoxic, inhibits breast cancer cell proliferation</td>
<td>H-S Kim et al. 2004; Murphy, 2002</td>
</tr>
<tr>
<td></td>
<td>Inhibits proliferation of prostate cancer cells</td>
<td></td>
</tr>
<tr>
<td>F11</td>
<td>Assists memory improvement</td>
<td>Z. Li, Guo, Wu, Li, &amp; Wang, 1999; Wu et al., 2003</td>
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<tr>
<td></td>
<td>Neuroprotective</td>
<td></td>
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</table>

**Effects on blood sugar and metabolism**

Numerous studies indicate that *P. quinquefolius* reduces postprandial glycemia in diabetic and non-diabetic human subjects in doses as low as 1g, suggesting a possible role for this species in complementing existing diabetic treatment (Vuksan et al., 2000a; Vuksan et al, 2000b; Vuksan et al, 2001). However, in one case when a different batch of *P. quinquefolius* from the same
supplier - but with a much lower ginsenoside profile - was tested, no such effect was observed (Sievenpiper, Arnason, Leiter, & Vuksan, 2003). In a separate study using *P. ginseng* no hypoglycemic effects were shown, rather there was a tendency towards elevated glucose (Sievenpiper et al., 2003). This finding was confirmed in a subsequent study of several species and types of ginseng in which the ginsenoside ratio (PPD:PPT) is posited as a significant factor in the variable glycemic response (Sievenpiper, Arnason, Leiter, & Vuksan, 2004). Yet in a recent study using five batches of Ontario-grown *P. quinquefolius* reduced postprandial glycemia and insulinemia were shown for three of the batches but not for the other two, and variations in ginsenoside content did not correlate with these differences (Dascalu et al, 2007). Studies in animals using *P. quinquefolius* leaves with high ginsenoside levels (referred to above) also demonstrated marked anti-hyperglycemic activity (J.-T. Xie et al., 2004), and similar results have been obtained using berry extracts of both *P. quinquefolius* and *P. ginseng* (Attele et al., 2002; J-T Xie, Mehendale, & Yuan, 2005). In a recent *in vivo* antidiabetic screening study of ninety botanical species, all three *P. quinquefolius* products (rhizome, leaf, berry) tested positive for lipogenic activity, however *P. ginseng* did not (Babish et al, 2010). Lipogenesis improves insulin sensitivity as new adipocytes take up more glucose and secrete fewer detrimental cytokines compared to the larger adipocytes they replace (Babish et al., 2010). Ginsenoside E has been identified as a specific hypoglycemic agent (Attele et al., 2002) although to date studies in humans do not support this effect (Reeds et al., 2011).

Ginsenoside Rb1 also suppressed food intake and body weight gain in obese rats, while improving glucose homeostasis. Modulation of associated signaling pathways and neuropeptides in the hypothalamus was observed (Xiong et al., 2010). Further studies with mice treated with polysaccharides extracted from the fruit suggest the polysaccharides are another potential component associated with anti-hyperglycemic activity for *P. quinquefolius* (Xie et al. 2004).

Molecular studies based on *P. ginseng* indicate ginsenosides suppress gene expression associated with the nuclear hormone receptors peroxisome proliferator-activated receptors (PPAR) *in vitro* and *in vivo* (Yoon et al., 2003; Banz et al., 2007). Furthermore, a specific ginsenoside Rb1 has been found to activate PPARγ - a transcription factor in adipogenesis - and increase expression of glucose transporters (GLUT) 1 and 4 *in vitro*. PPAR regulation has been linked to improved insulin sensitivity and reductions of lipid accumulation in muscle and liver (Banz et al., 2007) PPARs are also molecular targets for the anti-diabetic drugs known as TZDs (Kyu et al., 2006).

In sum these studies confirm a marked benefit on glycemic profiles at low doses for *P. quinquefolius* but the benefits for *P. ginseng* species are less consistent. While differences in ginsenoside levels and their ratios may influence the efficacy of *P. quinquefolius* it would appear that other components may also be involved (Sievenpiper et al., 2004).

**Diabetic renal damage**

Animal studies suggest that heat-processed *P. quinquefolius* (H-AG) extracts may have beneficial effects on renal damage associated with diabetic nephropathy. H-AG significantly decreased elevated urinary protein levels in streptozotocin (STZ)-induced diabetic rats, increased creatinine clearance and significantly reduced accumulation of advanced glycation endproducts (AGE) - a weaker effect on AGE was found with the unprocessed *P. quinquefolius* extract (H. Y. Kim, Kang, Yamabe, Nagai, & Yokozawa, 2007).
Cardiovascular effects
Preliminary studies on rats have demonstrated potential cardioprotective, anti-ischemic, antioxidant, calcium channel blocking and platelet aggregate moderating effects of *P. quinquefolius* (Yuan et al., 2010). Four months of dietary supplementation decreased oxidation damage to heart and muscle fibres with *P. quinquefolius* powder in rats (Fu & Ji, 2003). Promotion of angiogenesis to infarcted or ischemic regions by an extract high in saponins was shown to provide cardioprotection *in vivo* (Wang, Shi, & Yin, 2007). Ginseng species have ambiguous effects on angiogenesis – promoting wound healing on the one hand (dependent on angiogenesis) and inhibiting tumor growth via an antiangiogenic action on the other (Sengupta et al., 2004). These contrasting properties have been linked to specific ginsenosides (Rb1 as inhibitor and Rg1 as inducer of angiogenesis respectively). Rb1 angiogenesis inhibition has been linked to agonistic effect on estrogen receptor β (Papapetropoulos, 2007).

Memory and cognition
In contrast to the mild central nervous system (CNS) stimulant effects of *P. ginseng*, *P. quinquefolius* has a calming influence on the CNS (Yuan et al., 2010). There is a great deal of evidence demonstrating that ginseng species in general and specific ginsenosides have multiple effects in the CNS, an affinity for a wide range of receptors in the CNS (Yuan et al., 2010) and specific influence on hippocampal neurons (Rausch, Liu, Gille, & Radad, 2006; Jia et al., 2009). Animal studies show cognitive enhancing and neuroprotective actions for *P. quinquefolius*, and specifically for ginsenosides Rb1 and Rg1 – though possibly via different mechanisms (Benishin et al., 1991; Rudakewich et al., 2001). Rb1 facilitated release of acetylcholine from the hippocampus and increased choline in nerve endings (Benishin et al., 1991). Rb1, and to a less extent Rg1, extended the survival time of dopaminergic neurons against a selective neurotoxin (Radad et al., 2004). There is a particular focus on the use of ginseng products for prevention and treatment of degenerative brain disorders such as Parkinson’s and Alzheimer’s diseases (Jia et al., 2009; Radad et al., 2006; Rausch et al., 2006).

Common cold and immunity
Polysaccharide-rich extracts have been found to increase proliferation of spleen cells and macrophage activity in cell cultures as well as stimulate immunoglobulin G (IgG) *in vivo* and tumor necrosis factor (TNF) production from macrophages (Assinewe et al, 2002; Wang et al., 2001). Increased TNF- production also occurred in blood samples of three human volunteers following intake of *P. quinquefolius* (Zhou & Kitts 2002). CVT-E002 – a water soluble extract standardized for polysaccharides, is marketed under the patented name COLD-fX for the treatment of upper respiratory tract infections (Wang et al., 2004) and has been subjected to several clinical investigations (see ‘Clinical Studies' section below).

Mechanisms of anti-inflammatory activity have also been studied. Treating murine macrophages with *P. quinquefolius* extract quantified to contain 10% ginsenosides, LPS-induced nitrous oxide (iNOS) expression was inhibited, apparently by suppression of signal transducer and activator of transcription (STAT) cascade (Ichikawa et al., 2009).

Cancer
There has been considerable interest in the potential use of ginseng in cancer for many decades. Initially this interest focused mainly on using *P. ginseng* as an adjuvant to enhance efficacy and reduce side-effects of active cancer therapies such as chemotherapy and radiotherapy – based on
the herb’s reputation as an ‘adaptogenic’ agent (Jia et al., 2009). During the last decade there have been numerous investigations into the potential for *P. quinquefolius* to assist in the prevention and treatment of various forms of cancer.

Qi et al (2010) have explored potential structure-function relationships of ginsenosides in *P. quinquefolius*, identifying a number of possible cancer-prevention mechanisms including cell cycle modification, induction of apoptosis, and inhibition of angiogenesis and pro-inflammatory pathways. For a comprehensive review of studies and mechanisms involving ginseng and cancer see Jia et al. (2009).

**Breast cancer**
Using the standardized extract CNT-2000, studies on ER positive breast cancer cells showed dose-dependent decreases in cell and paradoxically an ability to induce expression of the estrogen-related gene pS2. There was no interference with the estrogen antagonist drug Tamoxifen when used concurrently, suggesting the possibility for synergistic interactions with conventional breast cancer agents (Duda et al., 1999). In a subsequent study the CNT-2000 extract was found to be an inducer of the p21 protein, a universal cell cycle inhibitor, in estrogen sensitive and insensitive breast cancer cell lines, suggesting a molecular mechanism of action for inhibition of breast cancer (Duda, Kang, Archer, Meng, & Hodin, 2001). Rice and Murphy confirmed *in vitro* inhibition of breast cancer cells, and further identified potent inhibition by a combination of ginsenosides Rc and Rh2. The two compounds appear to act via different mechanisms, Rc inhibiting progression of the cell cycle and Rh2 showing cytotoxic activity (Murphy, 2002). Further *in vitro* studies have elicited other potential molecular mechanisms, including induction of apoptosis through activation of a protease, and via protein kinase signaling pathways in cancer cells (King & Murphy, 2007).

**Other cancers**

Polyacetylenes in *P. quinquefolius* are cytotoxic to leukemia cells (Fujimoto et al., 1992). Ginsenosides Rg3 and Rh2 have been shown to inhibit DNA synthesis in prostate cancer cells, to induce cell detachment and to modulate protein kinases (H.-S. Kim et al., 2004). Rg3 can also inhibit metastasis of ovarian cancer cells *in vitro* (Xu et al., 2008). Miller, Delorme, and Shan (2009) conducted studies on mice with viral-induced tumors (erythroleukemia). Mice that were given 40mg/d of the CNT-2000 extract survived up to 50% longer compared to controls. When human colon cancer cells were exposed to *P. quinquefolius* extracts, cell proliferation and cell cycle progression was inhibited, an effect which was associated with both ginsenosides and polysaccharides (King, & Murphy, 2010).

**Endocrine effects**
The effect of ginseng on human hormones has long been a source of controversy. Laboratory investigations indicate ginsenoside Rb1 is an estrogen receptor agonist (Papapetropoulos, 2007; Leung et al., 2006). *P. quinquefolius* extract has also been shown to activate estrogen receptors however the effect was shown to depend on the extraction solvent used – aqueous extractions (which are polysaccharide rich) provide no estrogentic activity (King, Adler, & Murphy, 2006). Rgl1 activates glucocorticoid receptors (Lee et al., 1997) however this does not necessarily imply the ginsenoside acts like a steroid hormone (Leung & Wong, 2010).
Clinical Trials

Common cold
McElhaney et al. (2004) found that when COLD-fx was taken early in the “cold and flu” season the relative risk and duration of the common cold in a group of 43 elderly subjects was reduced compared to placebo by 48% and 55% respectively. In a larger trial of 323 subjects aged 18-65 years, the mean number of colds in the ginseng group was significantly reduced compared to the placebo group; severity of symptoms was reduced and the duration was also reduced by 2.4 days – these results are comparable to those of common antiviral drugs used for treatment of influenza (Predy et al., 2005).

Recently in a systemic review of five randomized clinical trials (four using COLD-fx, one Ginsana G-115- P. ginseng), the authors noted a consistent trend towards a lower risk of developing the common cold and evidence in two trials (both COLD-fx) that duration of colds and other acute respiratory infections was reduced by an average of six days. They concluded however that there is insufficient evidence to recommend ginseng extracts for prevention of the common cold (Seida, Durec, & Kuhle, 2009).

Memory and cognition
Recently an acute randomized double-blinded clinical study of 32 healthy young adults demonstrated significant improvement in working memory and other cognitive measures following ingestion of varying doses of P. quinquefolius extract (Cereboost™) standardized to 11.65% ginsenosides (Scholey et al., 2010).

Cancer
A randomized double-blind pilot study was conducted on 290 adult patients with a history of cancer-related fatigue, who were given ascending doses of 4-year old Wisconsin grown P. quinquefolius over eight weeks. The groups who received doses of 1,000 and 2000 mg daily appeared to have less fatigue compared to the group taking a placebo, as assessed by various validated scales (Barton et al., 2009). By contrast a randomized controlled crossover trial of ten healthy males given 1,125mg of CNT-2000 (a proprietary extract also known as North American Ginseng Extract (NAGE) containing 10% ginsenosides daily for five weeks failed to show significant effects on immune response as assessed by changes to white blood cell levels, lymphocyte proliferation or neutrophil oxidative burst (Biondo et al., 2008).

5. Modern Phytotherapy

Ginseng species are adaptogens – agents that increase general capacities to withstand situations of stress. P. quinquefolius is a noted adaptogen, inducing a reduction in stress and increase in physical performance over a period of time (Keville, 2000; Yarnell & Hooper, 2003). These adaptogenic effects are thought to assist in stress reduction via an influence on the hypothalamic-pituitary-adrenal (HPA) axis (Braun & Cohen 2010). Modern clinical applications include hormone modulation for menopausal women, reduction and prevention of tumors in breast cancer patients and overall support for people living with HIV (Yarnell & Hooper, 2003). Additional uses include improving cerebral circulation, reducing fatigue and supporting healthy heart function (Keville, 2000; Yarnell & Hooper, 2003).
The main therapeutic actions and clinical indications for *P. quinquefolius* are listed in Table 4.

**Table 4. Modern phytotherapeutic uses of *P. quinquefolius***

<table>
<thead>
<tr>
<th>ACTIONS</th>
<th>THERAPEUTIC INDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptogen</td>
<td>Weakness, deficient vitality, lethargy, convalescence</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>Anxiety, depression, improve memory and concentration</td>
</tr>
<tr>
<td>Sedative</td>
<td>Physical and mental effects of ageing, sexual inadequacy</td>
</tr>
<tr>
<td>Mild stimulant</td>
<td>Menopausal symptoms</td>
</tr>
<tr>
<td>Hypoglycemic</td>
<td>Adjuvant for patients on cancer therapies, HIV</td>
</tr>
<tr>
<td>Hepatoprotective</td>
<td></td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td></td>
</tr>
<tr>
<td>Stomachic</td>
<td></td>
</tr>
<tr>
<td>Tonic</td>
<td>Aphrodisiac</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Type II diabetes, hypoglycemia

Anorexia

Increase resistance to infections

Orthostatic hypertension

(Blumenthal, 2003; Green, 1991; Keville, 2000; Mills & Bone, 2000; Mitchell, 2003; Yarnell, Abascal, & Hooper 2003).

**Combinations**
With *Rehmannia glutinosa* (Gaertn.) DC. and *Astragalus membranaceus* Moench for debility, low grade fever and convalescence.
With *Turnera diffusa* Willd. Ex Schult. and *Serenoa serrulata* (Michx.) Hook.f. ex B.D.Jacks. for sexual inadequacy in males (Green, 1991).
With *Avena sativa* L. for nervous exhaustion

**Contraindications**
Avoid in conditions manifested by acute inflammation or high fever or irritability.

**Preparations and Dosage** (Blumenthal, 2003; Keville, 2000; Yarnell et al., 2003).
Powder: 0.30-10.0 grams, three times daily.
Decoction: 3-6g dried root simmered in 750-1000mL water.
Tincture: 2-4ml 3x a day
Standardized extract (5:1) – CNT2000: 2-300mg, 2-3 caps daily
TCM dose: 1-9g (Bensky & Gamble, 1993).

**Safety and toxicity**
*P. quinquefolius* is generally regarded as a safe herb, and is categorized as Class I: “herbs that can be safely consumed when used appropriately” by the Botanical Safety Handbook (McGuffin, Hobbs, Upton, & Goldberg, 1997). Most of the literature concerning ginseng and safety is based on *P. ginseng* which is not a reliable predictor given known phytochemical differences between the two species (Kitts & Hu, 2000). The National Toxicological Program performed short-term toxicity, long term carcinogenicity and genetic toxicology in vivo studies on ginseng species and found no evidence of toxicity (National Toxicology Program [NTP], 2004). In a Phase II clinical trial of 75 children with existing respiratory tract infections, safety data was generated and no significant adverse events were reported (Vohra et al., 2008). Charrios (2006) warns that the elderly may be at risk of exacerbating existing hypoglycaemia, and that diabetic subjects taking
*P. quinquefolius* should monitor blood glucose more frequently. She also refers to potential ‘severe effects’ of ginseng in general, but cites no examples or evidence (Charrios 2006). High doses do have the potential to cause nervousness or insomnia with both species (Jia et al., 2009).

*P. quinquefolius* does not appear to significantly affect cytochrome P450 enzymes, hence the risk of negative drug-herb reactions is relatively low. An *in vitro* study indicated inhibition of CYP3A4 was dependent on overall ginsenoside levels, however there was no such correlation with CYP2C9 (Luu, Foster, McIntyre, Tam, & Arnason, 2011). In one study on healthy human volunteers, a *P. quinquefolius* extract was combined with the HIV protease inhibitor drug Indinavir; there was no evidence of any pharmacokinetic interaction (Andriana et al., 2008).

**Regulatory Status**

*P. quinquefolius* is regulated in the U.S.A. as a Dietary Supplement. In Canada it is regulated as Food, if no therapeutic claims are made, and New Drug if claims are made.

6. **Sustainability**

**Ecological status-RTE status**

On a global scale, *P. quinquefolius* is listed as G3-G4. States vary in their assessment of the status of ginseng and not all states have up-to-date plant surveys. Connecticut, Minnesota, Massachusetts, and North Carolina list *P. quinquefolius* as of "special concern", Pennsylvania as vulnerable, Michigan and New Hampshire as threatened and Rhode Island as endangered. Tennessee lists *P. quinquefolius* as commercially exploited and does not include *P. quinquefolius* in its standard environmental review process. Landowners are advised that harvest is not sustainable (Tennessee Natural Heritage Program, 2008).

The Massachusetts DNR (n.d.) notes that across the nation, *P. quinquefolius* is considered to be a locally threatened species because of over-harvesting, primarily for export to China. (See Appendix-1)

**Harvesting & Collection regulations**

The collection, cultivation and trade of *P. quinquefolius* is governed at the county, state and federal level. The export of *P. quinquefolius* roots is regulated by the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) as an Appendix II species. Under the terms of CITES, the interstate and international trade is strictly controlled by the U.S. Fish and Wildlife Service. Interstate and international commerce records are required by the US Fish and Wildlife Service when permits are granted. These permits are limited to states that demonstrate adequate monitoring programs (U.S. Fish and Wildlife, 2011).

Continued approval for export from individual states is based on a determination by the U.S. Fish and Wildlife Service that exports will not be detrimental to the survival of the species.

**Table 5.** Harvesting regulations by state.

<table>
<thead>
<tr>
<th>Licensing required</th>
<th>Fee</th>
<th>Harvesting Time</th>
<th>Restrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>All states</td>
<td>USFWS requires state agreement for any export</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

15
<table>
<thead>
<tr>
<th>State</th>
<th>Requirements</th>
<th>Permits</th>
<th>Costs</th>
<th>Dates</th>
</tr>
</thead>
</table>
| PA    | 1. Vulnerable Plant license  
Required for harvesting & for cultivation except when gathered for personal use, pleasure or direct to the consumer via farmers market  
2. Harvester Certificate  
3. PA Export Certificate  
4. Dealer-Quarterly Reports  
5. March 31- Weight slip for any unsold ginseng | $50 | Sept. 1-Nov. 30 | Only plants with at least three leaves having five leaflets each may be harvested and only if all berries are red. Berries must be planted at that site. April 1 to September 1 no one in PA shall possess green harvested ginseng roots (Burkhart & Jacobson, 2004).  
As of May 2002, individual State Forest Districts stopped issuing collection permits for ginseng and goldenseal. To determine if ginseng/goldenseal collection is permitted on State Forest land, contact the District Office in which collection is desired. |
| NC    | 1. Dealers Permit  
a) Resident unlimited  
b) Resident limited (<100 lbs)  
c) non-resident  
2. Annual Dealer Reports  
3. Export certificate & fee  
4. Import certificate with state of origin  
5. Certificate of cultivated ginseng | $100, $50, $500 | Buying season Sept 1-Mar 31, Harvest Sept 1-Dec 1 | Dealers permit from the Plant Industry Division  
Ginseng may not be sold outside the season, no exceptions (the Statement indicating legal collection of ginseng from one's own land is no longer accepted)  
The certificate for cultivated ginseng - allows a grower to dig and sell ginseng at any time.  
The NCNFS (2005) sets the price per pound, offers permits from Sept 1 to Sept 30 which are good for 30 days only. Each permit allows a maximum of 3 pounds per person. |

The following states all have restrictions, licensing and permits which can be accessed on a state by state basis:

<table>
<thead>
<tr>
<th>State</th>
<th>Restrictions</th>
<th>Costs</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA</td>
<td>Protected from take (picking, collecting, killing...) and sale under the Massachusetts Endangered Species Act</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MN</td>
<td>Ginseng harvest regulated under Minnesota Rules, Chapter 6282. Seeds are required to be planted, plants must have 3 prongs.</td>
<td></td>
<td>Sept 1-Dec 31</td>
</tr>
<tr>
<td>KY</td>
<td>HB 362, the &quot;Ginseng bill went into effect June 8, 2011 There is $1,000 fine for buying ginseng from an unlicensed seller. Plants must have 3 prongs &amp; seeds must be replanted.</td>
<td></td>
<td>Aug 15-Dec 1</td>
</tr>
<tr>
<td>AL</td>
<td>Minimum age-3 prongs, seeds must be planted at site</td>
<td></td>
<td>Sept 1-Dec 13</td>
</tr>
<tr>
<td>AR</td>
<td>No harvesting on state lands, minimum age 5 years, 3 prongs, seeds must be planted at the site</td>
<td></td>
<td>Sept 1-Dec 1</td>
</tr>
<tr>
<td>GA</td>
<td>No harvesting on state lands, must have 3 prongs, seeds must be planted at the site</td>
<td></td>
<td>Aug 15-Dec 31</td>
</tr>
<tr>
<td>IL</td>
<td>No harvesting on state lands, minimum age 10 years, 4 leafed, planting encouraged at the site.</td>
<td></td>
<td>1st Sat in Sept- Nov 1</td>
</tr>
<tr>
<td>IN</td>
<td>Does not require seeds to be replanted, plants must have 1. 3 prongs, 2. a flowering or fruiting stalk or 3. 4 internodes on root. Note: allows harvesting during</td>
<td></td>
<td>Sept 1-Dec 31</td>
</tr>
<tr>
<td>State</td>
<td>Season</td>
<td>Requirements</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>-------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>Sept 1-Oct 31</td>
<td>Requires seeds to be replanted, plants must have 3 prongs. Allows harvesting state forests, but not in state parks or preserves.</td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>Aug 20-Dec 1</td>
<td>Harvesting allowed in state forests, not in parks. Plants must be 5 years old with 3 prongs.</td>
<td></td>
</tr>
<tr>
<td>MO</td>
<td>Sept 1-Dec 31</td>
<td>Seeds must be replanted, plants must have 3 prongs or fruiting stems.</td>
<td></td>
</tr>
<tr>
<td>NY</td>
<td>Sept 1-Nov 30</td>
<td>Seeds must be replanted, plants must have 3 prongs.</td>
<td></td>
</tr>
<tr>
<td>OH</td>
<td>Sept 1-Dec 31</td>
<td>Seeds must be replanted, plants must have 3 prongs.</td>
<td></td>
</tr>
<tr>
<td>TN</td>
<td>Aug 15-Dec 31</td>
<td>Seeds must be replanted, plants must have be 5 years old with 3 prongs.</td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>Aug 20-Oct 10</td>
<td>Seeds must be replanted, plants must have be 5 years old with 3 prongs.</td>
<td></td>
</tr>
<tr>
<td>VA</td>
<td>Aug 15-Dec 31</td>
<td>Seeds are not required to be re-planted and plants must have a minimum of 3 prongs.</td>
<td></td>
</tr>
<tr>
<td>WV</td>
<td>Sept 1-Nov 30</td>
<td>Seeds must be replanted, harvesting is limited to plants with 3 prongs.</td>
<td></td>
</tr>
<tr>
<td>WI</td>
<td>Sept 1-Nov 1</td>
<td>Plants must have 3 prongs &amp; mature fruit before they can be harvested, seeds must be replanted.</td>
<td></td>
</tr>
</tbody>
</table>

Export is currently regulated under the Convention on International Trade in Endangered Species of Wild Fauna & Flora Agreement.

Plants can only be exported if they are shown to be legally obtained in a fashion not detrimental to the survival of the species. States are given control over the management and certification for export of *P. quinquefolius* within their boundaries and are required to develop and implement a ginseng management program. They are required to submit specific export findings on a 3-year schedule (Michigan State University [MSU] Board of Trustees, 2004).

*P. quinquefolius* is on the United Plant Savers ‘at risk’ list and no wild harvest is recommended (Gladstar & Hirsch, 2000).

**Market Data - Harvesting Impact, Tonnage Surveys**


The following data is from the American Herbal Products Association.
In 2008 roots gathered in the wild were being sold for as much as $1,000/pound of dried root or about $4/root (Janiskee, 2008).

Cultivation
Habitat: Prefers rich hardwood forest with nutrient rich soils (Maine Department of Natural Resources [DNR], n.d.). Ginseng often occurs at the base of rock outcrops or on upland hill slopes where nutrient-rich soil has collected. Ginseng's medicinal and economic value varies according to how it has grown (Hertzog, 2010).

Cultivation: habitat
1. Wild Grown - These are plants that are naturally wild. They are considered to be the most valuable.
   Plant habitats are easily disturbed and plants may be damaged by campers, hikers or gatherers.
2. Wild-simulated- Seeds and rootlets are planted in a suitable habitat in its natural range.
3. Woods-grown- Seeds and rootlets are grown in woods similar in habitat to wild.
4. Field Cultivated - Seeds and rootlets are grown in fields with artificial shade. According to Herzog (2010) once ginseng has been grown and harvested from a field, it cannot be grown in that field again.

Table 6. Comparison chart (WildGrown.com, 2011)

<table>
<thead>
<tr>
<th>Origin</th>
<th>Wild Grown</th>
<th>Wild-Simulated</th>
<th>Woods-Grown</th>
<th>Field Cultivated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin</td>
<td>Occurs naturally</td>
<td>Seeds &amp; Rootlets planted</td>
<td>Seeds &amp; rootlets planted</td>
<td>Seeds &amp; rootlets planted</td>
</tr>
<tr>
<td>Habitat</td>
<td>Natural range in natural habitat</td>
<td>Within its natural range in suitable ginseng habitat</td>
<td>grown in woods similar to natural habitat</td>
<td>Grown in fields with artificial shade</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------------------</td>
<td>--------------------------------------------------</td>
<td>-------------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Cultivation</td>
<td>None</td>
<td>planting seeds &amp; rootlets only</td>
<td>Raised beds built for drainage</td>
<td>Intensive human cultivation</td>
</tr>
<tr>
<td>Fungicide</td>
<td>none</td>
<td>none</td>
<td>extensive</td>
<td>extensive</td>
</tr>
<tr>
<td>Harvest Method</td>
<td>Dug by hand</td>
<td>Dug by hand</td>
<td>Dug by machine</td>
<td>Dug by machine</td>
</tr>
<tr>
<td>Price/grade</td>
<td>highest</td>
<td>high</td>
<td>medium</td>
<td>low</td>
</tr>
<tr>
<td>problems</td>
<td>Selective harvests required to maintain population.</td>
<td>may need to remove some forest canopy</td>
<td>Pesticides &amp; fertilizers. Not organic</td>
<td>High labor costs Pesticides, fungicides, fertilizers subject to mold</td>
</tr>
<tr>
<td></td>
<td>Organic</td>
<td>Organic</td>
<td>Not Organic</td>
<td>Not organic</td>
</tr>
</tbody>
</table>

**Cultivation: Seeds**

Ginseng begins to produce berries (each with two seeds) in the third year. These should be cold stratified and some sources suggest storing in damp sand for a year before planting. The law may require that seeds from wild-gathered plants be planted immediately in the area surrounding the original plants. Gathered seeds may be planted from the end of September until the end of February, and will germinate April/May.

Plant seeds about 1/2" deep.

**Cultivation: Roots**

Ginseng does not reproduce vegetatively. Two-year old roots will produce berries the following fall.

Plant the roots about 1 1/2 inches deep, with the roots placed longways across the soil. Do not plant vertically. Cover the bed with mulch or rotten leaves.

**Cultivation: Crop Treatments**

Canada maintains a list of chemicals that are approved for use with ginseng.

1. "Glyphosate application is usually recommended in the first few weeks of April. For glyphosate to work properly, the weeds should be green and actively growing. However, it is important to ensure that no ginseng has emerged above the soil, or it could be damaged. There have also been reports in the past that glyphosate residues on the straw can damage ginseng if it emerges into the straw shortly after application. Closely examine the stage of ginseng emergence before applying glyphosate products" (Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA), 2011).

2. "Quadris can be applied at any time and should be applied before ginseng begins to emerge for maximum protection from Rhizoctonia. Quadris can be extremely toxic to some varieties of apple and crabapple. Do not apply where there is the possibility of drift onto apple trees. Application before a rainfall will improve penetration of the product to the root zone" (OMAFRA, 2011).

3. "The first application of Bravo should be applied when the ginseng has 20% emerged."
For more information on ginseng pest management, consult OMAFRA Publication 610 – Production Recommendations for Ginseng” (OMAFRA, 2011)

4. OMFRA (2011) also lists the following as approved for 2011:
   1) Switch 62.5 WG Fungicide for the control of Botrytis blight (*Botrytis cinerea*) and Alternaria leaf blight (*Alternaria panax*) on ginseng in Canada. Restrictions include: A maximum of two (2) applications per season can be made at an interval of 7 – 10 days if conditions remain favourable for disease development. In general begin applications prior to or at the onset of disease. Do not apply within 7 days of harvest for ginseng.
   2) Beleaf 50 SG Insecticide for the control of aphids. Allow a minimum of 7 days between applications. Do not apply more than 3 times per year.

**Harvesting**
Roots should be dug in the fall after the above-ground parts die back. Take care to dig the entire root with all of its branches. Wash as soon as possible, but do not scrub.

**Grower's Associations**
Appalachian Ginseng Foundation - http://www.a-spi.org/AGF/agfnl25.htm
Northwest Ginseng Growers Association - http://www.nginseng.org/home.html
Ontario Ginseng Growers Association (OGGA) - http://www.ginsengontario.com/

**Websites**

7. **Summary – some possibilities moving forward**
More than any other herbal species, *P. quinquefolius* plays a significant role in the history, culture and economy of the Appalachian community. Until recently, research into therapeutic applications has been focused on the Asian counterpart (*P. ginseng*), however the last decade has seen a dramatic rise in the number of peer-reviewed publications investigating the biology, phytochemistry, pharmacology of the indigenous species, as well as clinic effects on humans. Initiatives such as the American Botanical Council’s Ginseng Evaluation Program (Hall et al., 2001) which help to set standards for ginseng products are increasingly likely to focus on *P. quinquefolius*.

To date investigators have tended to focus on ginsenoside levels and their ratios in determining herb quality, and linking different ginsenosides to certain biological activities. It seems likely that levels of other constituents such as polyacetylenes and polysaccharides also influence quality and efficacy of *P. quinquefolius*, and that more focus should be placed on the use of whole root preparations, as well as of other plant sections. Now that a body of evidence is accumulating from laboratory and animal studies including safety data, there is a need for more human studies focusing on the potential benefits for cognition and memory, metabolic impairment, stress, fatigue and immune deficient disorders.
Finally, any research on the benefits to human health of *P. quinquefolius* needs to be paralleled by research on sustainable cultivation of this valuable Appalachian resource as well as policies that ensure the maintenance and growth of wild populations and native habitat.

8. References


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**Appendix 1.** Endangered, threatened, rare status

<table>
<thead>
<tr>
<th>Global</th>
<th>G3-G4</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>US federal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sc special concern</td>
</tr>
</tbody>
</table>

| CT |
| Sc special concern |

<p>| MI |
| threatened S2S3 |</p>
<table>
<thead>
<tr>
<th>State</th>
<th>Status</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maine</td>
<td>S3</td>
<td>Maine Department of Conservation, Natural Areas Program, Rare Plants. P. Quinquefolius last observation date: 2002</td>
</tr>
<tr>
<td>RI</td>
<td>SE</td>
<td>Rhode Island, one extant population. SE, G4, Rhode Island Rare Plants (2007) <a href="http://www.rinhs.org/wp-content/uploads/ri_rare_plants_2007.pdf">Link</a> one extant population</td>
</tr>
<tr>
<td>MA</td>
<td>special concern</td>
<td>Natural Heritage and Endangered Species Program. 2008. Massachusetts list of endangered, threatened, and special concern species. Westborough, MA: Massachusetts Division of Fisheries and Wildlife accessed at <a href="http://www.mass.gov/dfwle/dfw/nhesp/species_info/mesa_list/mesa_list.htm">Link</a></td>
</tr>
</tbody>
</table>