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Review

Eleutherococcus senticosus (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look

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Abstract

The adaptogen concept is examined from an historical, biological, chemical, pharmacological and medical perspective using a wide variety of primary and secondary literature. The definition of an adaptogen first proposed by Soviet scientists in the late 1950s, namely that an adaptogen is any substance that exerts effects on both sick and healthy individuals by 'correcting' any dysfunction(s) without producing unwanted side effects, was used as a point of departure. We attempted to identify critically what an adaptogen supposedly does and to determine whether the word embodies in and of itself any concept(s) acceptable to western conventional (allopathic) medicine. Special attention was paid to the reported pharmacological effects of the 'adaptogen-containing plant' *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Araliaceae), referred to by some as 'Siberian ginseng', and to its secondary chemical composition. We conclude that so far as specific pharmacological activities are concerned there are a number of valid arguments for equating the action of so-called adaptogens with those of medicinal agents that have activities as anti-oxidants, and/or anti-cancerogenic, immunomodulatory and hypocholesteroletic as well as hypoglycemic and choleretic action. However, 'adaptogens' and 'anti-oxidants' etc. also show significant dissimilarities and these are discussed. Significantly, the classical definition of an adaptogen has much in common with views currently being invoked to describe and explain the 'placebo effect'. Nevertheless, the chemistry of the secondary compounds of *Eleutherococcus* isolated thus far and their pharmacological effects support our hypothesis that the reported beneficial effects of adaptogens derive from their capacity to exert protective and/or inhibitory action against free radicals. An inventory of the secondary substances contained in *Eleutherococcus* discloses a potential for a wide range of activities reported from work on cultured cell lines, small laboratory animals and human subjects. Much of the cited work (although not all) has been published in peer-reviewed journals. Six compounds show various levels of activity as anti-oxidants, four show anti-cancer action, three show hypocholesterolemic activity, two show immunostimulatory effects, one has choleretic activity and one has the ability to decrease/moderate insulin levels, one has activity as a

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radioprotectant, one shows anti-inflammatory and anti-pyretic activities and yet another has shown activity as an antibacterial agent. Some of the compounds show more than one pharmacological effect and some show similar effects although they belong to different chemical classes. Clearly, *Eleutherococcus* contains pharmacologically active compounds but one wishes that the term adaptogen could be dropped from the literature because it is vague and conveys no insights into the mechanism(s) of action. If a precise action can be attributed to it, then the exact term for said action should obviously be used; if not, we strongly urge that generalities be avoided. Also, comparison of *Eleutherococcus* with the more familiar *Panax ginseng* C.A. Meyer (Araliaceae), 'true ginseng' has underscored that they differ considerably chemically and pharmacologically and cannot be justifiably considered as mutually interchangeable. Accordingly, we recommend that the designation 'Siberian ginseng' be dropped and be replaced with '*Eleutherococcus*'. In the case of both *Eleutherococcus* and true ginseng, problems inherent in herbal preparation use include inconsistencies not only in terms of indications for use, but in the nomenclature of constituent chemical compounds, standardization, dosage and product labeling. Finally, our re-examination and fresh interpretation of the literature on *Eleutherococcus* and comparison with true ginseng shows that the potential for a scientifically more complete and defensible exploitation of these plants will be better served by investigating and considering them in a context that consciously ignores the fact that the word 'adaptogen' was ever invented.

Keywords: Adaptogen; Adaptogenic activity; *Eleutherococcus senticosus*; *Panax ginseng*; Lignans; Anti-cancer agents; Anti-oxidants; Placebo effect; Saponins; True ginseng; 'Siberian ginseng'

1. Introduction

There has been a dramatic revival in recent years in the use of herbal preparations for the treatment of a wide range of ailments (Eisenberg et al., 1998). Some products are being recommended for use as 'specifics' to treat particular illnesses or conditions much like conventional synthetic medications are prescribed in North America, Western Europe and the rest of the economically developed world (Tyler, 1993, 1994; Blumenthal et al., 1998). Others, however, are being promoted for more general use. For example *Echinacea* (purple cone-flower) is being offered as a general immune system booster (Blumenthal et al., 1998). Other herbal preparations are being marketed for oral use on a regular basis for the prevention of rather unspecific potential conditions or ailments in a prophylactic way. (Why herbal product use is enjoying a significant resurgence in economically developed countries is beyond the scope of this article but for a few different perspectives reference may be made to Astin 1998; Humber and Almeder, 1998, and Krikorian, 1998).

Galenical preparations or herbal mixtures similarly intended for non-specific use(s) were formerly referred to as 'tonics' (especially when they were in liquid form and contained some ethanol but indeed even if they were not liquid preparations) (Carson, 1961). However, the expression 'tonic' is hardly to be found in the contemporary American herbal medicine literature (see Mowrey, 1993 as an example of an exception). Although it would be wrong to assign the origin of non-specific and restorative tonic preparations to any single culture or geographical region, widespread use seems to be most firmly entrenched in the traditional medical systems of east, northeast, south and southeast Asia.

Contemporary descriptors for what used to be called tonics are suggestive and are more or less tied to what they are supposed to do (Mowrey, 1993). But closer scrutiny of the etymology shows them to be as unrevealing as the word tonic and every bit as non-committal as to their pharmacological action. Expressions like adaptogens, restoratives, harmonizers, adjustives, corrective adjuncts, alteratives, vitalizers, preventives or preventatives, oriental adjustive remedies, protectives and even the possibly more scientific-sounding phrase 'inducers of states of non-specifically increased resistance' (SNIR) are freely bandied about even though they have until recently been rather vaguely informative at best, even to those professionally versed in clinical pharmacology

and therapeutics. Nevertheless, there are a fair number of traditional medical systems that have incorporated routine use of adjustive preparations or treatments into their health care delivery systems. All of these preparations are used to keep the body in proper tune, so to speak. In the traditional-Hindu medical (Ayurvedic) System of India they are called *rasayana* (for rejuvenation), in the traditional-Malaysian and Indonesian medical systems they are called *jamu*, in the fung shui system of China in which one seeks to balance man and nature to create a harmonious environment they are called *zi bu or hui fu* (meaning tonic and restorative respectively in Mandarin) and in Russian *toniziruyuzhie sredstva* (meaning tonic substances). Each of these either connotes or means 'that which makes new again', or 'that which helps restore one's youthful state of physical and mental health, as well as helps expand a state of happiness'.

We will focus in this review largely on one such 'non-specific' agent that is enjoying considerable use namely, *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. This plant is often referred to in the USA as 'Siberian ginseng'. As we shall see, and contrary to some contentions that *Eleutherococcus* is the ancient source of an 'adaptogen' or 'adaptogenic activity', its extensive use probably derives only from the mid-1950s and early 1960s. Introduction of the Soviet pharmacopoeial extract of *Eleutherococcus* into the USA is said to have occurred only in 1971 (cf. Sonnenborn and Hänsel, 1993).

Despite our dissatisfaction with the words 'adaptogen' and 'adaptogenic activity' ('why' will emerge in the course of this review), we have perforce used them here in connection with this non-specific 'herbal supplement' for several reasons. The main one is that the word adaptogen developed as a result of clinical pharmacological studies made with *Eleutherococcus* and hence it is arguably the model source of 'active' compounds, whatever that may actually come to mean. And, although we will concentrate on *Eleutherococcus*, it will be evident that any special concepts that might emerge from our analysis should be broadly applicable to any preparation of, or from, a natural source purported to have adaptogenic qualities (Wagner, 1987, 1990, 1995; Wagner et al., 1994).

2. *Eleutherococcus* and the adaptogen concept

2.1. 'Ginsengs'

The family to which *Eleutherococcus* belongs, the Araliaceae, includes some 84 genera which are native to Asia, the Malay peninsula, Polynesia, Europe, North Africa and the Americas (Wielgorskaya and Takhtajan, 1995). Only the genus *Panax* and some species of *Aralia* are herbaceous; the rest are woody vines, shrubs or trees. For many centuries the peoples of China, Korea and Japan have used roots and leaves of *Panax ginseng* C.A. Meyer (mainly roots however). Following others we will refer to the *P. ginseng* plant as 'true ginseng'. (In our view the designation 'Asian' or 'Oriental ginseng' is less helpful since *Eleutherococcus* is also 'Asian' or 'Oriental'). True ginseng has been valued for many years as a folk remedy for a wide variety of conditions and ailments as well as a tonic or alterative etc. (Goldstein, 1975; Fulder, 1980a,b, 1993; Baranov, 1982; Leung, 1984; Carlson, 1986; Chong and Oberholzer, 1988; Duke, 1989).

Most readers will readily appreciate that true ginseng is reasonably well known outside east Asian cultures. In fact, because many individuals, scientists and lay people alike, readily recognize the word ginseng, it has fostered a proliferation of terms aiming to capitalize on the positive connotation of anything designated a 'ginseng'. For instance, the roots and leaves of *Withania somnifera* L. (Solanaceae) have been used for centuries in Ayurvedic medicine under the name *ashwagandha* (Atal and Schwarting, 1961; Chemexcil, 1992), and has in some quarters outside India taken on the name of 'Indian ginseng'. So far as we can determine, *Withania* has never been referred to as 'Indian ginseng' in the scientific literature on Indian medicinal plants (Bhatnagar et al., 1948; Chadha, 1985; Ambasta, 1986; Chemexcil, 1992; Sivarajan and Balachandran, 1994; Rege et al., 1999). Similarly, *Pfaffia paniculata* Kuntze (*Hebanthe paniculata* Mart.) (Ama-

ranthaceae, sometimes called 'suma') has been referred to outside Brazil as 'Brazilian ginseng' (or outside Bolivia as 'Bolivian ginseng'). It is well-known in Brazil as an aphrodisiac but it is used equally extensively for it's alleged anti-diabetic properties (Subiza et al., 1991). Pfaffic acid has been isolated from dry root of the plant and has been reported to be effective as an inhibitor of growth of cultured cancer cells, specifically melanoma (B-16), Hela (S-3) and Lewis lung carcinoma cells at a concentration of 4–6 μg/ml (Takemoto et al., 1983). *P. paniculata* has been marketed in the USA as a component of 'rainforest ginseng' along with other allegedly synergistic botanical ingredients like *Lepidium meyenii* (Cruciferae) (sometimes referred to as 'Peruvian ginseng' or 'maca', and sarsaparilla (mainly from *Smilax officinalis* L. (Smilacaceae) but nowadays recognized as deriving from any of several species of *Smilax* (cf. Leung and Foster, 1996).

Preparations of true ginseng are frequently marketed and labeled according to geographical origin, e.g. Korean ginseng, Chinese ginseng, Japanese ginseng as well as whether the processed root is red or white. So-called red ginseng, produced by a special Chinese process of steaming etc. that turns the normally creamy-colored fresh root 'reddish' (Veninga, 1976; Zaricor, 1980) has been reported as more 'stimulating' and effective (Fulder, 1980b). 'Tien Chi' or 'Sanchi' ginseng generally listed in the commercial or advertising 'literature' as from *Panax Notoginseng* which grows in southern China is marketed for uses similar to but also slightly peripheral to those of true ginseng, *P. ginseng*. The North American member of the genus, *Panax quinquefolius* L. called 'American ginseng' is sometimes marketed in the forms 'Woodsgrown' and 'Wild'). As mentioned above, *E. senticosus* referred to as 'Siberian ginseng' by some authors since it was first exported from Siberia in the Soviet era, and the designation seems to have persisted. Within the borders of the former USSR, however, 'Siberian ginseng' has always been referred as 'eleutherokokk' perhaps best expressed in English simply as '*eleutherococcus*', or '*Eleutherococcus'*, or even as adopted by some, '*eleuthero'* (cf. e.g. Tyler, 1994). It will be seen why the designation '*eleuthero gingseng*' (c.f. Veninga, 1976; Zaricor, 1980) is inappropriate. But the main point is that it has never been called 'Siberian gingseng' by the Soviets. Indeed, in Russia and other republics of the former USSR, *E. senticosus* has never been viewed or used as an exact substitute for true gingseng, *P. gingseng* (c.f. e.g. Baranov, 1982).

In any case, each of these 'ginsengs', whether one appreciates their common or invented commercial/marketing names or not, seems to be valued for a given purpose or in a particular health problem context, and some preparations even combine them. Interestingly, 'American ginseng' root is highly regarded in east Asia for its allegedly excellent properties. Indeed, oftentimes it is more valued than the root of the true ginseng of the 'Orient' and hence has had a long history of being considerably more expensive (Garman, 1898; Kains, 1906; Harding, 1908; Williams, 1957; Graham, 1966; Hardacre, 1968; Proctor and Bailey, 1987; Singer, 1990). It is, however, not generally used as a substitute for the kinds of tonic effect associated with true ginseng. Instead, it is used in their medical system to treat conditions related to 'heat' and 'dryness', such as fevers and coughs. Leung (1984) points out that 'American ginseng' is especially popular with the southern Chinese (e.g. the Cantonese). The action of 'American ginseng' root is more normally equated with that of the leaves of true ginseng. Fulder (1980b) on the other hand emphasizes that in the Orient *Eleutherococcus* normally has the reputation of a less effective substitute for true ginseng. Interestingly, there has hardly been any tradition at all of using American ginseng in the USA; indeed it never was a popular home remedy even in the areas where it grows wild (Garman, 1898). Its use is increasing, however, by virtue of the device of being marketed in mixtures of true ginseng in combination with other 'ginsengs' (see later in this review). Mention must be made, however, of the recognition of certain medicinal qualities of 'American gingseng' root by Native American Indians (Krochmal and Krochmal, 1973; Veninga, 1976)

As might well be expected of a plant that has been known and nominally valued for centuries (at least by some, mainly by those who could

afford it), wild populations of *P. ginseng* have long since been over-exploited. Natural habitat loss has also contributed to the problem of unavailability. Shortages led to inflated prices long ago. To increase availability, sporadic efforts were made in various countries to cultivate true ginseng. It has been cultivated in Korea for some years and is the basis of a substantial domestic and export industry (Fulder, 1993). Cultivation of true ginseng has even been undertaken in a number of locations in the New World, e.g. in Canada especially in the Province of Ontario, near Ottawa, and places such as Wisconsin, USA.

Wild *P. ginseng* was very scarce in the Soviet Far East (eastern Siberia) as well as in Korea and adjacent regions as far back as the 1950s–1960s. Recognizing that it takes a very long time (order of a minimum of 6 years and preferably longer) to cultivate a 'quality' true ginseng root efforts were made by Soviet workers to identify an alternative and plentiful plant source that would have similar pharmacological activity and 'tonic' properties. It was in this context that scientists in the USSR turned their attention from *P. ginseng* to *E. senticosus* as part of a screening of the Araliaceae family (Brekhman, 1968). As it turns out, this is the only species in the genus which grows in the territories of the former USSR and which has a habit and gross morphology somewhat similar to true ginseng. Both the roots and leaves of *E. senticosus* are reported to be the source of 'adaptogens'.

Eleutherococcus (from the Greek *eleutheros* meaning 'free', and *kokkos* meaning 'pip' or 'seed', more precisely a pyrene in botanical terminology) is a thorny shrub that grows in the Russian Far East, the Amur Region, Primorksy Krai, Sakhalin, and also in Northeast China, Korea and Japan. The thorniness, reflected by the specific epithet senticosus, an adjective meaning in Latin 'full of briers or thorns', has led to the common names in Russian of 'thorny *Eleutherococcus*' (eleutherokokk koljuchii), 'untouchable' (nedotroga), 'devil's bush' (dyavol'skii kust), 'wild pepper' (dikii perets) or even 'thorny bearer of free berries' (svobodnojagodnik koljuchii) (see Mashkovsky, 1988 and Fig. 1). (Incidentally, no one seems to have seriously concerned himself/herself with establishing whether they are in the strictest sense, anatomically, prickles, that is sharp outgrowths from the outer epidermal layer, as in the case of roses which produce prickles not thorns, or whether they are spines, i.e. small thorns or aborted branches or whether they are some other kind of epidermal appendage or emergence formed from both epidermal and subepidermal tissues.) The far less common Russian designation '*tajozhnyi koren*' (taiga root) derives from its association as an understory plant in the northern coniferous evergreen forests of the subarctic region (the so-called taiga bordered on the north by the treeless tundra and on the south by the steppe). (One of the common names of *Eleutherococcus* root in German is Taigawurzel (taiga root, cf. e.g. Bladt et al., 1990); another is Teufelskrallenwurzel (devil's claw root, not to be confused with the root of *Harpagophytum procumbens* (Burchell) DC of the sesame family, Pedaliaceae, also called Teufelskralle (cf. Sprecher, 1977) but nowadays usually with the qualifier 'Südafrikanische' (Teufelskralle) in an attempt to avoid potential (inevitable?) mix-up (Blumenthal et al., 1998). Both are direct translations from the Russian.)

According to some authorities there are about 15 species of *Eleutherococcus*, and all are found in eastern Asia from the Himalayas to Japan. As mentioned above, in the territories of the former USSR there is only one species, *E. senticosus*. On the other hand, some claim there are about twice as many valid species. For instance the New Royal Horticultural Society Dictionary of Gardening (1992) says that there are about 30 species.

Eleutherococcus seems to have been first collected some time between 1830 and 1841 by Porphyrii Yevdokimovich Kirilov (1801–1864?). Kirilov was the physician appointed to the 11th Russian Ecclesiastic Mission to Peking (arriving there via Mongolia in 1830 to replace the 10th Mission which had been there since 1820). After years of service and botanizing, Kirilov returned to St Petersburg in 1842. Bretschneider (1898) lists *E. senticosus* and *P. ginseng* among those many plants collected by Kirilov but only described botanically later by CA Meyer, Ruprecht, Regel, Maximowicz (all of the Imperial Botanical Gar-

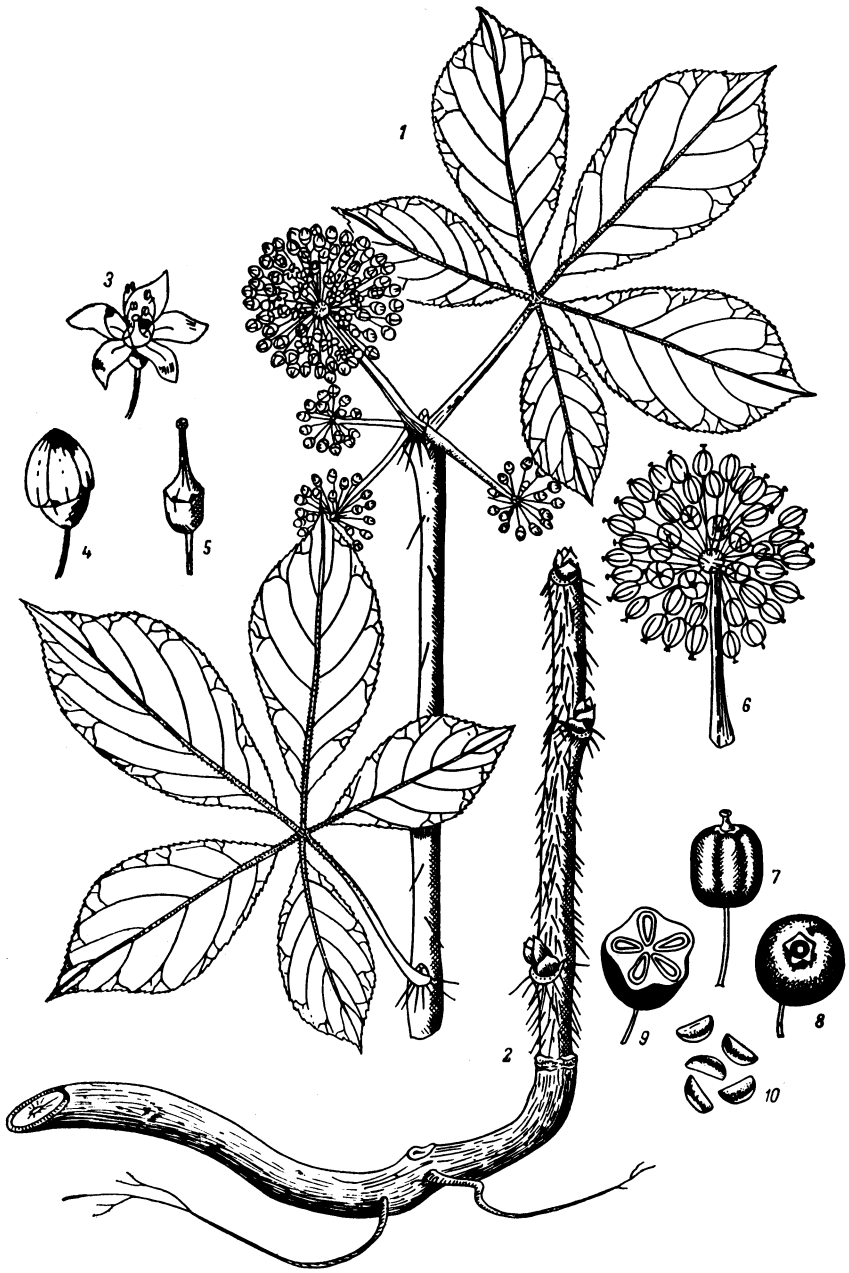


Fig. 1. Diagrammatic representation of *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Araliaceae). (1), flowering branch; (2), portion of a root cutting used as a propagule showing spiny shoot and lateral buds that have been generated from it; (3), open flower; (4), floral bud; (5), pistil; (6), inflorescence; (7), lateral view of the fruit; (8), view of fruit from above; (9), transverse section of the fruit; (10), seeds. This species is a shrub to about 7 m but it is usually much shorter, usually about to 2 m. The stems are erect, sparingly branched and densely thorny (prickly, spiny?) or even unarmed (form *inermis* Komar). The thorns point backwards. The leaves are three–five foliate, petioles to 12 cm, finely prickly or unarmed. The leaflets are 13–7 cm stalked, elliptic-obovate to oblong. Diagram reproduced from Brekhman (1968) page 11.

den, St. Petersburg). In fact, Carl Ivanovich Maximowicz (1827–1891), the Conservator of the Imperial Botanical Garden in St Petersburg, and later the Head Botanist and supervisor of the herbarium of the Imperial Botanical Garden in St Petersburg, even raised *Eleutherococcus* from seeds that had been sent back to the garden during one of his own trips to the Far East, Manchuria (cf. Bretschneider, 1898 and Fig. 2). Significantly, no mention seems to have been made concerning the use of *Eleutherococcus* as a medicinal plant but this tentative statement merits validation if only for historical purposes.

Only many years later after renewed attention had been paid to *Eleutherococcus* was it claimed by Brekhman (1968) that *Eleutherococcus* had identical or even superior pharmacological effects to those long-attributed to true ginseng (Baranov, 1982). *Eleutherococcus* certainly was and still is easier to find and collect from the wild than its true ginseng relative. During the 1950s and 60s

Fig. 2. Carl (Johan) Ivanovich Maximowicz (1827–1891). From Wittrock, 1905 Tafel 82. With permission, Bergius Foundation of the Royal Swedish Academy of Sciences, Stockholm.

Eleutherococcus became the subject of a number of studies from the perspective of its geographical and topographical distribution, as well as the conditions under which it grew (Brekhman, 1968). (Parenthetically, it was also learned that it is considerably easier to cultivate *Eleutherococcus* than true ginseng, see Halstead and Hood, 1984 for a compilation in Latin script of references to some of the Russian literature).

Finally, this seems to be a good place to comment on the botanical nomenclature for *Eleutherococcus*. The valid botanical name is *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Soejarto and Farnsworth, 1978). Some literature however, some of it fairly recent, still refers to this same plant under an older, now-relegated-to-synonomy binomial as *Acanthopanax senticosus* with or without the botanical authority (Rupr. et Maxim. ex Maxim.) Harms (see Lui and Staba, 1980; Wagner, 1987, 1990 as examples) or [Rupr. et Maxim.] Harms (see e.g. Bladt et al., 1990). Nevertheless, *Eleutherococcus* and *Acanthopanax* are now generally considered different genera in the Araliaceae. Although *Eleutherococcus* and *Acanthopanax* were merged by Harms in 1898 it has since been established that the oldest validly published name, *Eleutherococcus*, should be retained (Soejarto and Farnsworth, 1978). (Mention will be made later that use of *Eleutherococcus* as a medicinal plant is rather recent; its use under the designation of 'adaptogen' is certainly recent. It is beyond the scope of this review article to resolve the question whether this polymorphic genus might in fact have a considerably older usage as an 'adaptogen' or for other purposes than its more recent history implies. The use of common names in the older herbal literature (e.g. Chinese) underscores a widespread problem in identification of a given plant and linking it rigorously with a specific use. (A table provided by Bladt et al., 1990 that lists some of the morphological features of some 11 'species' of *Eleutherococcus* emphasizes how trivial the nominally distinguishing features are!) We predict that the satisfactory resolution of this problem will prove to be far more complex than has been presented by Halstead and Hood, 1984).

3. Adaptogens and the Soviet connection

In the late 1940s (ca. 1947) scientists at the Far Eastern Division of the Soviet Academy of Sciences in Vladivostok, Siberia began to study compounds that brought about a state of 'non-specifically increased resistance' of an organism (*nespetsificheskaya soprotivlyaemost' organisma*) in experimental animals and humans (date cited in Wagner et al., 1994; Wagner, 1995). Later, Grinevich (1990) described searching for prospective medicinal plants by use of a computer. A number of complex remedies from the 'Cannon of Medicinal Science' by the great Persian scientist, philosopher and physician Avicenna (Abu Ali ibn Sina), Indian recipes from Ayurvedic medicine, Chinese, Korean and Japanese prescription recipes were compared and contrasted. The criteria for the comparison were the frequency of use of a certain plant in a recipe, the purpose of use of a certain plant in a recipe, and how many plants with the same pharmacological effect were used in a recipe. This search showed that certain plants were used in preparations of the different medicinal systems, even though the countries involved were sometimes geographically quite distant.

According to the late Professor Israel Itskovitch Brekhman (1921–94) (Brekhman, 1968) and Brekhman and Dardymov (1969), it was Dr Nikolai Vasilievich Lazarev (Lazarian in Armenian) (1895–1974), then the leading figure in Soviet pharmacology and toxicology and a developer of a number of new drugs, who first proposed to the scientific and medical community in the mid-1950s that substances which were able to bring about an increased non-specific resistance be called 'adaptogens' (adaptogen in Russian, presumably based on the Latin *adaptare*, to adjust or fit, and 'gen' from the Greek *genes* or born of, or produced by. Incidentally, it is generally regarded as a barbarism to combine Greek and Latin roots in a single word). Terms like 'revitalizing therapies' or 'tonic herbs' which contain 'immunopotentiating principles' or 'immunomodulatory substances' (*immunopotentsial'nyi effekt*/*immunomoduliruyuzshie sredstva*, respectively, in Russian) are not uncommon in the Soviet literature of the period. Not only are such 'adaptogenic plants', with *Eleutherococcus* as the model, viewed as sources of agents that enhance tolerance to stress, they have even been promulgated of as sources of substances that have preventive and anti-cancer activity as well as some other positive activities (Lazarev, 1955; Kupin et al., 1986). It was a slow process however before the idea of an adaptogen now adopted by at least some Western researchers of complementary and alternative therapies, namely that adaptogens are a group of substances reputed to offer varying degrees of protection against internal and external stressors, crept into western consciousness (and vocabulary).

Indeed, an extensive search of the medical, chemical and pharmaceutical literature shows that the word 'adaptogen' is really very rarely used. It is not readily retrievable through any of the normal computer searches of scientific literature. In fact, we have not found a definition of any sort in any dictionary, medical or otherwise, English or Russian (Müller, 1989; Akzhigitov et al., 1992; Howlett et al., 1993). 'Pharmacosanation' (*pharmakosanatsiya*) is another term which was used extensively in connection with work or discussions on adaptogens. While it is not a term that is used in the West, in Russian public health and medical science circles it is understood and defined as 'that part of pharmacology that deals with the effects of biologically active substances in food or medicines that increase stability against various unfavorable effects, that promote prophylaxis and normalize functions…' (Brekhman, 1980). Viewed from this perspective, there is a special condition characterized by the body's ability to achieve a state of increased resistance to the damaging action of various substances and agents. Significantly, this state is believed to be attained by gradual (even over a period of months) exposure to the action of an adaptogen against unfavorable factors in the external environment, or even single-dose administration of certain medicinal substances (i.e. an adaptogen or mixture of adaptogens). (For brief summaries of the Russian literature of that period in English see Brekhman, 1980; Halstead and Hood, 1984 or Kamen, 1988 although the latter appears to be more promotional than scientific in intent.)

These various properties of an adaptogen were expanded upon and enumerated in outline form by Brekhman in 1968 and were published in his multidisciplinary publication on *E. senticosus* and *P. ginseng* (Brekhman, 1968). According to Brekhman (1968)

1. The action of an adaptogen should be innocuous and cause minimal disturbance to the normal physiological functions of an organism. It must be absolutely harmless;
2. an adaptogenic agent should not be active only in a specific context or against a particular background. It must have a broad therapeutic spectrum of action;
3. the action of an adaptogen has to be non-specific, that is to say, resistance to a wide variety of action of harmful factors, whether of a physical, chemical or a biological nature, has to increase. In other words, the action of an adaptogen has to be more intense as unfavorable changes occur in an organism;
4. an adaptogen has to have a normalizing or stabilizing action independent of the direction of previous changes.

According to Lazarev and Brekhman, adaptogenic activity can be brought about by quite different substances of very different origin (Brekhman and Dardymov, 1969). Moreover, they probably have different mechanisms of action, but the same pharmacological effect. These many chemical and physical non-specific factors nominally increase the state of resistance of the human body to outside irritants and stresses. Lazarev called this bodily state 'the state of increased non-specific resistance' (*sostoyanie povyshennoi nespetsificheskoi soprotivlyaemosti* in Russian).

From the foregoing, few trained in conventional modern western medicine would be in a position to imagine in very much detail what an adaptogen does or does not do so far as the pharmacologist is concerned, but more importantly, what its specific mechanism of action might be (cf. e.g. Wagner et al., 1994; Rege et al., 1999). In fact, one could easily argue that the concept of an adaptogen as initially proposed by the Soviet workers is imprecise, even vague, and certainly does not lend itself to classification within any broad category of medicinal substance or pharmacological activity. Indeed, one might elect to emphasize and argue that the alleged qualities or properties of an adaptogen as put forward by the inventors of the term apply equally well to a placebo (Frank and Frank, 1991; Harrington, 1997; Shapiro and Shapiro, 1997). We will return to this point later.

Be all this as it may, the writings of Brekhman and his colleagues reflect confidence that they had shown that an adaptogen works for a those who are 'not well', especially in those cases where there is a need to increase immunity after surgery, or to facilitate convalescence after a serious disease. Equally interesting, however, is that Brekhman et al. purported to have shown that an adaptogen works in healthy individuals as well and that adaptogens help to maintain a healthy state by minimizing the effects of harmful external factors (cf. Brekhman, 1968).

After the term adaptogen was first coined, its use was limited so far as its applicability to substances of plant origin was concerned, to the responses brought about through the activity of *Eleutherococcus* extracts after oral administration. It was later extended to any product of botanical origin that enabled the body to counteract negative effects of 'stress', in the broadest sense of that word. Thus, plants such as *Aralia mandshurica* Rupr. & Maxim. and *Aralia cordata* Thunb. (from the family Araliaceae), *Rhaponticum carthamoides* (Willd.) Iljin and *Carlina biebersteinii* Bernh. (Compositae), *Rhodiola rosea* L. from the family Crassulaceae and *Shizandra chinesis* (Turcz.) Baill. from the family Shizandraceae were also advocated by the Soviet scientists as having adaptogenic activities (Brekhman and Dardymov, 1969; Baranov, 1982). In that early period, a wide range of individuals appear to have taken up the use of *Eleutherococcus*, including élite athletes. Soviet-era coaches are reputed to have incorporated regular use of eleutherokokk preparations into their athlete-training protocols (Brekhman, 1968; Fulder, 1980a). Presumably this was because *Eleutherococcus* nominally enhanced ergogenic activity. (Ergogenic is an adjective derived from the Greek word 'ergo' for work and 'gen', meaning 'production of'. It is usually

Fig. 3. Photographs of Soviet postage stamps, both 1973. (a) *P. ginseng* (Araliaceae), 2 kopecks. At the top 'Medicinal Plants'. On the left, the common name in Russian, i.e. common ginseng (zhen'shen' obyknovennyi); (b) *Oplopanax elatum* (Araliaceae), 1 kopeck. At the top 'Medicinal Plants'. On the left, the common name in Russian, 'zamanikha vysokya' (literally 'tall enticer'). Personal collection of one of us, ADK.

defined as an ability to increase potential for work output (see e.g. Williams, 1995). Familiarity with *Eleutherococcus* as an ergogen and adaptogen entered Europe through encounters with Soviet-bloc trainers, coaches, athletes, sports physicians etc. (cf. Fulder, 1980a; Asano et al., 1986; Kamen, 1988). That is not to say that Soviets did not value the medicinal properties of plants like *P. ginseng* and other Araliaceous plants like *Oplopanax elatum* Nak. Indeed, postage stamps to commemorate their use were even issued (see Fig. 3a, b).

A number of studies on the effects of *Eleutherococcus* were carried on human subjects and some of them were done on mice. Subjects were exposed in clinical studies of various designs to stresses such as noise, high altitudes, the running of long distances and being forced to perform some rather complex psychomotor tests. In this research, treatment with *Eleutherococcus* was chosen as the experimental variable and controls comprised true ginseng and placebo (colored water or aqueous alcoholic solutions). Endurance and oxygen uptake were used in some of the trials as fitness indicators. The experiments showed that human subjects who took *Eleutherococcus* extract were enabled to perform tasks most effectively. Those who took ginseng extract performed better than those who took colored water but somewhat worse than the *Eleutherococcus* group (Brekhman, 1968 *passim*). Some of the tests and interpretation of the clinical results pre-dated common use of the word 'adaptogen'. Based on what has been said above, it may be speculated that the authors attributed their findings to what came to be called the 'adaptogenic properties' of *Eleutherococcus* as well as true ginseng without going through extensive or exhaustively detailed reasoning of what might be happening mechanistically.

Nevertheless, in order to appreciate better how the adaptogen concept and the use of adaptogens became so readily integrated into health care practice during that period, or even today might be integrated in the West, some attention will now be devoted to differences between Western-style, conventional medicine and 'Eastern' medicine.

4. Western-style and eastern medicine: a world apart?

It may be argued that contemporary western medicine views illness as due to what might be termed for comparative purposes, and for lack of a better term, a 'malady' at the organ, tissue, cellular, subcellular and molecular level. Treat-

ment is accordingly based on attempting to effect a 're-alignment', or simply physical or psychological treatment of symptoms of a discomfort rather than the cause of it (Clouser et al., 1997; Thagard, 1999). By contrast, traditional Chinese medicine, and similar systems of 'traditional Asian' e.g. east Asian, southeast Asian, south Asian and central Asian (e.g. Tibetan) Medicine, each portray illness or a disease as the result of a dysfunction of the whole system. Here, misalignment is due to the reaction of an organism to 'irritants' of different origin, both internal and external. Therefore, any treatment assigned to a particular disease is normally targeted at the whole system. The contemporary Chinese view of a disease most likely originated from Buddhism, where one of the main postulates is that everything and everybody are interconnected (Hsiao, 1980; Leung, 1984; Huang, 1993; Bivins, 1997).

Stated another way, a disease is the result of external and internal stress(es) on the human body. External stresses may be of a chemical, physical, biological, psychological and/or social origin. Any enumeration of internal stress would necessarily include heredity and, of course, certain diseases or tendencies towards pathological processes can be passed on from generation to generation through the genes (Mulvihill, 1991; Cotran et al., 1994; McKusick, 1998). The age and sex of a person, the nature and type of activity of their nervous system, their so-called constitution, the ability or inability of a given body to cope with stress are also 'internal' and accordingly, all play a significant role as well from the 'Asian' perspective (see Weiss, 1987 for example for a good discussion of karma doctrine and how it relates to the Ayurvedic system of India as a determinant of disease etiology). Interestingly, the ancient Greeks, the originators of modern western medicine, similarly viewed a disease as a manifestation of an internal/external imbalance of bodily 'humors', and treated it accordingly (Grmek, 1998).

Most would agree that a 'state of good health' or what is increasingly being referred to in the USA as 'wellness' is a relative state. Many different factors affect this 'healthy state' in humans (Clouser et al., 1997). Substances classified as chemical irritants or factors which trigger various pathological pathways fostering manifestation of a disease state may also be interpreted as substances that intrude upon, bother as it were, or have an adverse or positive affect on a given system after contact. Chemical irritants include such things as toxins, venoms, allergens and various compounds, natural or synthetic (see the journals 'Natural Toxins' (1992) and Journal of Natural Toxins (1992)).

Microorganisms, viruses, mycoplasmas etc. may be cited as obvious examples of biological or biotic factors, the invasion of which can also cause various diseases (see Table 1 for an admittedly simplistic yet hopefully insightful summary of these concepts). Similarly, modern pathology views a 'disease' as the result of cellular injuries and cell death caused by biological, chemical and physical factors (Cotran et al., 1994).

Table 1
Some factors that are known to be involved in the origin of disease

Factor	Example
Chemical factors	Toxins, venoms, various allergens
Biological factors	Microorganisms — bacteria, fungi, mycoplasmas and viruses and products of their metabolism and/or degradation
Heredity	Bodily 'constitution' and inheritance of the propensity to develop various disease states
State of the nervous system	Bodily 'constitution' and so-called 'choleric', 'melancholic', 'phlegmatic' and 'sanguinic' types of nervous system (see text for further details on these terms)
Other(s)	Physical factors such as external injuries which may lead to a disease. The affect of external irritants on an unstable mental system resulting in the triggering of a pathological pathway. Age and sex of a subject which pre-disposes him/her to certain diseases etc.

It may be appropriate as well to say a few words here on how immunity is variously viewed. Allergens are substances of microbial and fungal etc. origin and their toxins, and any of their degradation products. They also include non-microbial and fungal proteins like those ingested in foods, from air-borne pollen, plant and animal fibers and hairs and any other factor (cf. Table 1). Such allergens bring about an 'inflammation'; this is the first stage leading to an imbalance in the human immune system (Mulvihill, 1991). The imbalance turns on the body's cellular machinery to 'fight foreign intruders'. If, for example, the cellular signaling system is overworked, it will lead to an allergic reaction. Or, if a body is not able to 'neutralize' an intrusion, a disease will develop as the result of decreased immunity. In brief then, immunity represents a critical measure of the resistance of an organism to stresses from the external environment, stresses that can result in a diseased state. Immunity could be described equally well as the defensive and adaptive reaction of an organism to stress and insult at the cellular and molecular levels (Sanglier, 1993). Recall that according to the inventors of the adaptogen concept, Lazarev and Brekhman, a substance with adaptogenic activities should be able to help maintain, and when it is necessary, to correct the immune state of an organism.

Irrational nutrition and malnutrition constitute very important stresses, and may be viewed as one category of biochemical irritation to an organism. Irrational nutrition may cause such well-known diseases as obesity, diabetes, atherosclerosis and various types of hypo- or even hypervitaminoses (Cotran et al., 1994). Malnutrition can also cause conditions such as anemias and vitamin deficiencies such as pellagra (deficiency of vitamin B_3), rickets (deficiency of vitamin D), beriberi (deficiency of vitamin B_1) and scurvy (deficiency of vitamin C) (see e.g. Mason, 1996; Wilson, 1998).

In addition to the role of genetics and heredity, it will also be appreciated that what is sometimes referred to as the 'constitution' of a person can be an important internal 'cause' of illness. Historically, three types of constitution or disposition of a human body have been categorized: astenic (weak/thin), normal, and hyperstenic (strong/thick). Astenics and hyperstenics are said to be prone to develop certain diseases (D'iakova and Rudenko, 1993). The well-known Russian physiologist Ivan Petrovich Pavlov (1849–1936) actually distinguished four types of higher nervous activity: choleric (irritable or easily angered), melancholic (slow or gloomy), phlegmatic (quiet, calm, even apathetic) and sanguinic (cheerfully optimistic). Pavlov noted that animals (humans included) reacted differently to irritants and, therefore, were prone to diseases in different ways (Pavlov, 1927). The age and sex of a person are, on this view of the relationship of disposition to susceptibility to illness, also 'internal' causes and can pre-dispose one to certain diseases. For instance, women have breast cancer and thyroid enlargement much more often than men. On the other hand, prostatic cancer is necessarily restricted to males. Men also seem to have more ulcers of the digestive tract than females. Also, both men and women are prone to different types of chronic disease, including cancer, depending on the country in which they live, their diet and lifestyle habits (cf. e.g. Rothschild, 1981).

In modern western medicine precise therapies are definitely preferred over agents that purport to have broad or non-specific therapeutic action. Simply stated, there is no need to take medication when it is not required. Moreover, agents that serve to 'normalize' and 'stabilize' generally are thought to do so by virtue of their ability to minimize or eliminate any potentially adverse psychological component, such as worry. (Hence the widespread use of anxiolytic agents or tranquilizers in many western societies –see e.g. Casey, 1996; Scahill and Skrypeck, 1997). Therefore, only a malfunctioning organ or system needs to be treated or 'cured'. If in the course of treatment, or afterwards, yet another problem arises, say one that is brought about by the dysfunction of a different system, it too is treated. This is perhaps the single most distinctive feature of the approach taken by practitioners of modern, conventional medicine in dealing with illness (Poynter, 1963 and refs. cited therein). Granted the foregoing, it is interesting to contemplate that an agent that alleviates or eliminates a disease or general 'condition' could qualify to be called a 'non-specific' or

'cure-all' or even a 'panacea' in western medicine. No less significantly such an agent would also qualify to be called a placebo (Morris, 1992; Shapiro and Shapiro, 1997).

The reader will recall by way of comparison, that in the tradition of holistic medicine historically so assiduously followed in traditional 'Oriental and Asian Medicine', particularly by practitioners of Chinese medicine and its traditional Japanese derivative, 'kampo', the view is that illness is a result of a violation of the balance between an organism and its environment, both internal and external (Bensky and Gamble, 1986; Bensky and Barolet, 1990). That is, when an organism is affected by an irritant or intruding element, the whole organism becomes involved and a disease occurs (Saks, 1997). Again contrast that if you will with the Western viewpoint that maintains that a disease is a pathological state of a cell, tissue, organ, or system and, ultimately the whole organism. Such a pathological state causes a fundamental, i.e. constitutional defect in the affected organ or a systematic dysfunction which perforce originated on a cellular level, indeed at a subcellular and molecular level (Mulvihill, 1991; Cotran et al., 1994).

5. Our approach to the adaptogen 'problem'

Given our interpretation of the facts sketched above, we believed from the outset that it would not be a casual effort to conceptualize what an adaptogen would 'do' medically or how it would 'work' from the perspective of contemporary modern western medicine. Therefore, we sought first to examine as wide a range of scientific literature as could be obtained, some rather difficult to locate and access, including many Russian language publications, in an attempt to ferret out as much information on adaptogens as we could. We examined the history, and then we examined the context of the clinical use of adaptogens, and evaluated the experimentation alleging benefits from use. And, proceeding from this essentially historical perspective, we sought to compare and contrast what an adaptogen 'really' is, does, or is expected to do for a user, with more conventional, 'specific' medicines. This was all done against a range of terms, some familiar, others not-so-familiar, used throughout the history of medicine and pharmacy in the hope that we might reach a better understanding of an adaptogen's 'nature'. We also attempted to compile as complete a list as possible of the secondary chemical constituents of *Eleutherococcus* which have been reported to have pharmacological activity. Finally, we tried to compare systematically and from several perspectives the chemical composition of *Eleutherococcus* with that of true ginseng to see if any common features could be disclosed. This, then, is what this paper is all about. And to prepare the reader for what follows, we categorically state here that despite any shortcomings of the definition of adaptogen, or even the concept of an adaptogen, and there are many, there is considerable evidence that supports the view that *E. senticosus* is a potentially important source of clinically active substances. We provide and develop the evidence and present rational arguments for our stance in the following sections.

6. Results

6.1. Chemical composition of Eleutherococcus

Not surprisingly, it was the same workers who carried out clinical research on *Eleutherococcus* and adaptogens, namely Brekhman et al., who were the first to carry out phytochemical studies on the plant. Working in the late 1950s and 60s in Siberia, chemical investigations were made along side the pharmacological work (Brekhman, 1968, 1976). Somewhat later, in the 1970s and 80s, the study of the chemical composition of *Eleutherococcus* was taken up by several other groups, namely in Germany, Japan and China (see Table 2). It may be stated, incidentally, that whereas phytochemical studies on *Eleutherococcus* seemed at the outset to have attracted a fair amount of interest, this interest seems to have latterly waned considerably. A recent search of the literature through the NAPRALERT (NAtural PRoduct ALERT) database carried out to supplement our

Table 2
Some chemical components of *Eleutherococcus senticosus* and their reported pharmalogical effects

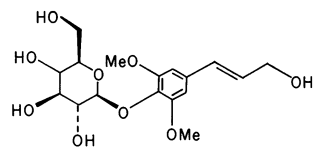
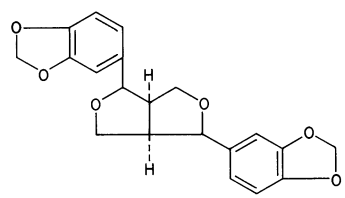
Chemical constituent	Botanical source(family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structure
Syringin*	*Acanthopanax senticosus* (Araliaceae), (*E. senticosus*)	Protectant against damage from radiation[a,b]. Fewer deaths occurred in mice after X-ray irradiation (400 rads); decreased leucopenia, improved white blood cell count and thrombocyte level in human workers after exposure to unspecified radioactive substances (Ruijun et al., 1990)	 Syringin ($C_{17}H_{24}O_9$)
Syringin	Syringin from *Tinospora cordifolia* (Menispermaceae); natural product chemistry division of regional research laboratory, Jammu Tawi, India	Immunopotentiating/immunostimulatory effect[c]. Inhibited immunohaemolysis of antibody-coated sheep erythrocytes by guinea pig serum (Kapil and Sharma, 1997)	See above structure
Sesamin	Not specified	Hypocholesterolemic effect[d]. Induced hypocholesterolemia (especially low-density lipoproteins and cholesterol, which are risk factors for human atherosclerosis) (Hirata et al., 1996)	 Sesamin ($C_{20}H_{18}O_6$)
Sesamin	Mixture of sesamin and episesamin provided by Suntory, Osaka, Japan	Anti-cancer effect[c]. Showed 36% reduction in 7,12-dimethylbenz[a]anthracene-induced mammary cancer in female rats at 12 weeks after uptake (Hirose et al., 1992)	See above structure
Sesamin	Crystalline mixture of sesamin and episesamin (1:1), from Takemoto Oil and Fat, Gamagori, Japan	Immunostimulatory effect[c]. Decreased liver enlargement caused by ethanol intake; increased the concentration of IgG [γ-immunoglobulin] (Nonaka et al., 1997)	See above structure

Table 2 (*Continued*)

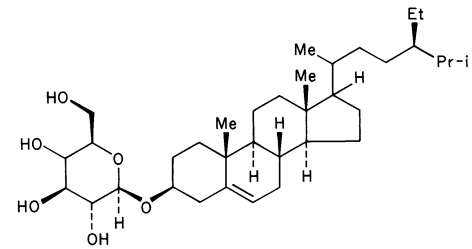
Chemical constituent	Botanical source (family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structure
Sesamin	Mixture of sesamin and episesamin prepared and purified from refined sesame oil by authors	Improved impaired liver function in rodents caused by 1% ethanol or carbon tetrachloride (100 mg/kg)[f] (Akimoto et al., 1993).	See above structure
β-sitosterol (many synonyms, e.g. β-sitosterol-3-β-D-gluco-pyranoside)	Sigma Chemical, St Louis, MO, USA	Anti-cancer effect[e]. Inhibited growth of human colon cancer cells (HT-29) by activating sphingomyelin cycle (Awad et al., 1998)	 β-Sitosterol β-glucopyranoside ($C_{35}H_{60}O_6$)
β-sitosterol	*Cyperus rotundus* (Cyperaceae). Unclear whether isolated by authors.	Anti-inflammatory and anti-pyretic effect[g] similar to that of acetylsalicylic acid (Gupta et al., 1980)	See above structure
Sitosterol	Not specified	Hypocholesteremic effect[d]. Administered doses reduced cholesterol absorption in man (Heinemann et al., 1993)	See above structure
β-sitosterol and β-sitosterol-3-β–D-glucoside	β-sitosterol was obtained from 'Dr Esteve' Laboratory; β-sitosterol and β-sitosterol-3-beta-D-glucoside was prepared by semi-synthetic method by the authors	Anti-hyperglycemic effect, insulin-reducing effects mostly due to β-sitosterol[h]. Increased fasting plasma insulin level; decreased fasting glycemia after oral administration. Both compounds increased glucose-induced insulin secretion. Overall improvement in results in oral glucose tolerance test (Ivorra et al., 1988)	See above structure
β-sitosteryl-β-D-gluco-pyranoside	Not specified	Hypocholesteroletic effect[d]. Sitosterol glucoside was able to bind to low density lipoproteins (LDL) and decreased vascular permeability; also showed hemostatic effect (Sugiyama and Seki, 1991)	See above structure

Table 2 (*Continued*)

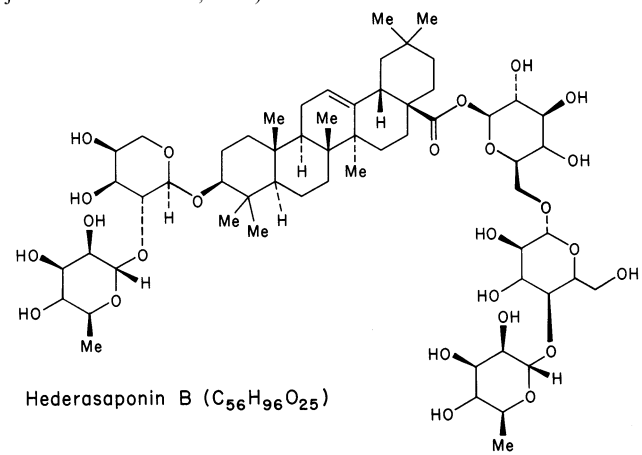
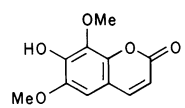
Chemical constituent	Botanical source (family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structure
Hederasaponin B	*Hedera helix* L. (Araliaceae)	Anti-leishmanicidic effect but not confirmed (Majester-Savornin et al., 1991)	 Hederasaponin B ($C_{56}H_{96}O_{25}$)
Isofraxidin (6,8-dimethoxy-7-hydroxy-coumarin)	*Micrandra elata* (Euphorbiaceae)	Anti-cancer activity[e]. Cytotoxic in lymphocytic leukemia in mice (Borris et al., 1980)	 Isofraxidin ($C_{11}H_{10}O_5$)
Isofraxidin	*Artemisia abrotanum* L. (Asteraceae)	Choleretic effect[i] when administered at 25 mg/kg (Danielak et al., 1973)	See above structure

Table 2 (*Continued*)

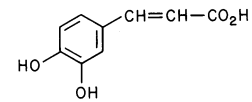
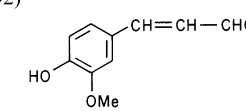
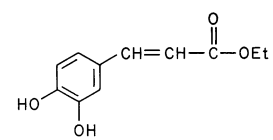
Chemical constituent	Botanical source (family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structure
Caffeic acid	Sigma Chemical, St. Louis, MO, USA (Catalogue # C-0625)	Anti-oxidative effect[a]. Anti-xanthine oxidase activity. Anti-tumor, anti-gout, anti-hepatitis activity (Chan et al., 1995)	 Caffeic acid ($C_9H_8O_4$)
Caffeic acid	ICN Biomedical Irvine, CA, USA	Anti-oxidative effect[a]. Caffeic acid and other phenolic compounds from green tea showed reduction of nitric oxide production in C6 astrocyte cells (Soliman and Mazzio, 1998)	See above structure
Caffeic acid	Not specified	Antibacterial effect[j]. Inhibited growth and production of aflatoxin by *Aspergillus parasiticus* (Aziz et al., 1998)	See above structure
Caffeic acid	Not specified. Apparently they quantified caffeic acid along with other phenolic compounds in a given ingested food source	Anti-oxidative and anti-cancer effects when administered at 206 mg/d[a,e] (Radtke et al., 1998)	See above structure
Caffeic acid	Not specified	Anti-oxidant and anti-cancerogenic effects[a,e]. Inhibited tumor promotion in vivo and vitro with murine peritoneal macrophages when they treated with tumor promoters and produced superoxide anions (Kaul and Khanduja, 1998)	See above structure
Coniferyl aldehyde	Clove buds from Takasago Perfumery. The compound was obtained from clove bud oil in the authors' laboratory	Anti-oxidative effect[a]. Anti-oxidant against skin damage induced by UV light-derived hydroxyl radicals (Taira et al., 1992)	 Coniferyl aldehyde ($C_{10}H_{10}O_3$)

Table 2 (*Continued*)

Chemical constituent	Botanical source (family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structure
Caffeic acid ethyl ester	Prepared by authors	Anti-oxidative effect[a]. Protectant against single stranded DNA breaks in Chinese hamster V79 cells caused by hydrogen peroxide. Overall protection against cell damage (Nakayama et al., 1996)	 Caffeic acid ethyl ester ($C_{11}H_{12}O_4$)

* Given as the active component; however it is unclear from the context of the work whether or not the compound was tested alone.
[a] Anti-oxidant.
[b] Active against radioactivity damage.
[c] Immunostimulant.
[d] Hypo-cholesteroletic.
[e] Anti-cancer agent.
[f] Improved liver damaged caused by alcohol (anticirrhotic).
[g] Anti-inflammatory.
[h] Hypoglycemic.
[i] Choleretic (or cholagogic).
[j] Antibacterial.

own extensive search, disclosed only 233 references on chemical composition and pharmacological effects on animals and human subjects from 1924 to April 1998. More recent searches up until final proof submission for press shows that nothing has been published since then to change the facts or our interpretations. In short, we believe we are fairly up-to-date.

An intrinsic feature of *Eleutherococcus* chemistry, which is more or less common to all phytochemistry is that the relevant chemical nomenclature is not uniform. Even today, there is no universally adopted system or formally accepted protocol for giving common or trivial names to similar or even identical chemical compounds from various plants. Utilizing a botanical generic name followed by a traditionally accepted suffix to refer to various classes of components has only served to generate confusion in our view, although all appreciate that it is arguably intrinsically necessary to give a crude mixture or a fraction some sort of name so as to allow preliminary pharmacological and clinical studies to go forward. After all, jargon is the currency that facilitates scientific communication. For instance, we see true ginseng (*P. ginseng)* saponin compounds referred to with equal frequency as panaxosides or ginsenosides Ra, Rb, Rc etc. (the various 'Rfs' deriving historically from the relative positions of spots (relative to the front' = Rf) on plates after separation and disclosure via thin layer chromatography, see e.g. Lui and Staba, 1980). Thus, Rg has been sometimes treated or referred to as a single compound from true ginseng. However, the designation Rg has also been used to designate total saponin content in ginseng. *E. senticosus* provides an equally good example of nomenclature and identity problems. According to Brekhman (1968) and Dardymov (1976), eleutheroside A is identical to the sapogenin daukosterin (originally identified from carrot, *Daucus)*, which is 3-O-β-sitosterin glucoside, and eleutheroside *B* is syringin (a lignan isolated initially from lilac, *Syringa*), which is the 4-β glucoside of sinapyl alcohol. However, some, for instance Ruijun et al. (1990), have apparently preferred to refer to eleutheroside A as the lignan syringin. Undoubtedly some of the 'chemical synonymy' is due to precipitous publication of names and structures without adequate study of the literature. In other words, the chemistry problem derives largely from the fact that pharmacological or clinical effects of these phytochemicals are often defined earlier than the chemical composition is rigorously determined and verified. Mention was just made that eleutheroside A is identical to daucosterol. Likewise eleutheroside B_4 is identical to sesamin; eleutheroside B_1 is isofraxidin which is more accurately known as isofraxidin-7-O-β-L-glucoside, or syringaresinol; eleutheroside E is (−)syringaresinol-4,4′-O-β-D-diglucoside, also identical to acanthoside D; eleutheroside E_1 is (−)-syringaresinol-O-β-D-monoglucoside and so on (cf. e.g. Bladt et al., 1990).

It is perhaps understandable that some sort of name is deemed useful to convey a preliminary indication of what the active components might be provided the compounds in question are novel. One is less sympathetic to hasty publication when the structures are rather well known. The practice of giving a name to compounds in a way that implies that they are somehow distinctive to the genus or species in question is unfortunate from several perspectives, not the least of which is that many plants, including rather unrelated genera, synthesize similar or identical secondary compounds (cf. e.g. Romeo et al., 1996). It is regrettable that the Soviet phytochemists classified from the outset a wide range of very different substances from *Eleutherococcus* under the heading 'eleutherosides', even though some of them ought to have been recognized as fairly prevalent in the plant kingdom. In the case of true ginseng at least, 'ginsenosides' typically belong to the same group of substances. In an attempt to bring some kind of order to this situation Wagner (1980) has since urged that the major eleutherosides be divided into two classes:

1. the triterpenoidal saponins which are glycosides of oleanolic acid (historically referred to as eleutherosides I, K, L, and M);
2. the phenylpropane derivatives (e.g. eleutherosides B, B_1, D and E) most of which are glycosylated (Sonnenborn and Hänsel, 1993).

The problem is that it is very difficult to retroactively make 'corrections'. We have avoided the problem in large measure by attempting to adhere to the known chemistry but as we shall see, this does not always work.

Table 2 lists a number of secondary compounds from *Eleutherococcus* reported by various authors. The substances are not only found in *E. senticosus* but they occur in a diverse range of plants belonging to various families. The table also shows that compounds from *Eleutherococcus* fall into different chemical groups with various reputed pharmacological effects. Some of the compounds bring about rather different responses at the clinical level. Most of them, like betulinic and caffeic acid, sesamin and syringin, vitamin E and β-carotene, sitosterol and daucosterin, have been shown to exert anti-oxidative and/or anti-cancer effect(s) on one or more cultured cell lines.

The literature shows that the constituents listed have been tested in widely accepted medical tests and assays, and that their alleged effects have generally been more or less validated by different authors. Even though much of the pharmacological data listed in Table 2 derives from investigations using compounds or substances obtained from plants other than *E. senticosus*, we emphasize that each of them occurs in *Eleutherococcus*. Thus, *Eleutherococcus* and the other plant sources cited share a common chemistry, and hence we presume a potential common pharmacology, so far as one or other constituent is concerned. Unfortunately, there is virtually no data on the quantities of a given class of secondary compounds that a given species of the group we are interested in might produce. These compounds include but are not limited to phenylpropanoids (e.g. syringin, caffeic acid, sinapyl alcohol, coniferyl aldehyde), lignans (e.g. sesamin, syringoresinol and its glucoside), saponins (e.g. daucosterol, β-sitosterol, hederasaponin B), coumarins (e.g. isofraxidin and its glucoside) and vitamins like vitamin E, and provitamins like β-carotene.

It has been suggested (but not proven obviously) that lignans, like many other secondary products, are evolutionarily-derived by elaboration of the phenylpropanoid pathway for a plant's own 'benefits', as its own immunoprotection and protection, as it were, from harmful free radicals (see Lewis and Davin, 1994). Significantly, a number of lignans have been reported to have anti-tumor activity in animals and humans. For example, the lignan podophyllotoxin and related compounds have been studied for their anti-tumor activities and this has led to the design of new anti-cancer drugs (Ayres and Loike, 1990; Daley et al., 1998; Donelli et al., 1998; Subrahmanyam et al., 1998). However, podophyllotoxin is most widely used today to treat venereal warts, condyloma acuminata (White et al., 1997; Tyring et al., 1998; Jablonska, 1998)! *Eleutherococcus* not only synthesizes lignans such as syringin, syringoresinol and sesamin, but also makes and accumulates lignan precursors such as cell wall-bound hydroxycinnamic acid-caffeic acid and other intermediate compounds of lignan synthesis such as coniferylaldehyde. These precursors have been shown to have significant anti-cancer activity in various laboratory assays as well (Taira et al., 1992; Chan et al., 1995; Aziz et al., 1998; Kaul and Khanduja, 1998; Radtke et al., 1998; Soliman and Mazzio, 1998).

6.2. Eleutherococcus versus true ginseng (P. ginseng)

During our study of the literature on adaptogens, it became apparent that it would be instructive to compare and contrast *Eleutherococcus* and true ginseng from as many vantagepoints as possible, especially their phytochemistry and pharmacology. As mentioned above, the use of true ginseng in herbal preparations as an 'adaptogen' long before the term was coined goes back many centuries (cf. e.g. Lee, 1956; Chen, 1973; Goldstein, 1975; Fulder, 1980b; Leung, 1984; Fulder, 1993).

Table 3 lists to the extent possible the secondary chemical composition of *P. ginseng*. Unlike the summary data presented in Table 2 on *Eleutherococcus*, the pharmacological information in Table 3 derives exclusively from publications relating to true ginseng. It has been claimed (Fulder, 1980b; Zaricor, 1980) and reported later with experimentally supported data by Konoshima (1996) that the active compounds of red ginseng

Table 3
Some chemical components pf *P. ginseng* and their reported pharmalogical effects

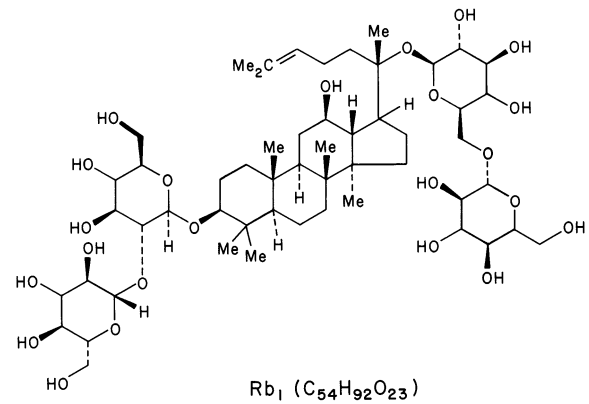
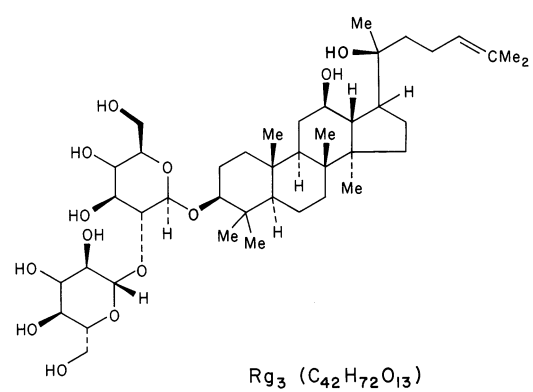
Chemical constituent	Botanical source (family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structures
Ginsenosides Rb_1 and Rg_3	Not specified	Anti-oxidative effect; prevention of senile decline[a]. Protected neuronal cells from overproduction of nitric acid (Kim et al., 1998d)	 Rb_1 ($C_{54}H_{92}O_{23}$)  Rg_3 ($C_{42}H_{72}O_{13}$)

Table 3 (*Continued*)

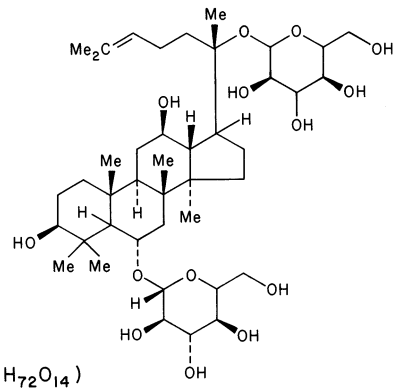
Chemical constituent	Botanical source (family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structures
Ginsenosides Rb_1 and Rg_1	Rb_1 and Rg_1 from Korea Ginseng and Tobacco Institute, Taejon, Korea	Modulated methamphetamine-induced behavior (hyperactivity and conditioned place preference) in pre- and post-synaptic dopaminergetic receptors (Kim et al., 1998b)	 Rg_1 ($C_{42}H_{72}O_{14}$)
			see above for structure of Rb_1
Ginsenoside Rg_1	*P. ginseng* (Araliaceae) not clear whether unpurified saponins were isolated by authors or provided by someone else	Anti-impotence effect[b]. Increased incidence of copulatory behavior in mice when administered at 2.5, 5, 10 mg/kg (Yoshimura et al., 1998)	See above for structue of Rg_1
Ginsenoside Rg_1	Rg_1 from Korea Gingseng and Tobacco Institute, Taejon, Korea	Nominal preventive effect and agent for treatment of adverse effects of morphine[c]. Inhibited catecholamine secretion at presynaptic sites (Kim et al., 1998a)	See above for structure of Rg_1

Table 3 (*Continued*)

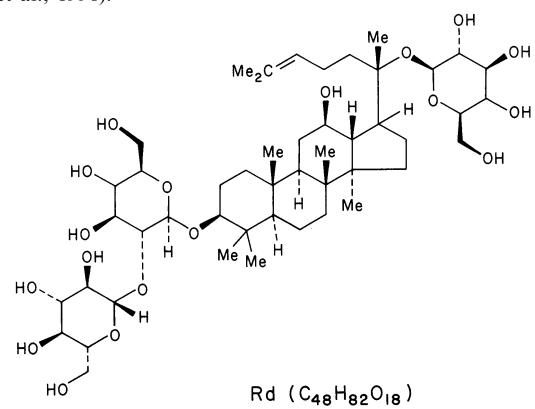
Chemical constituent	Botanical source (family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structures
Ginsenoside Rd	Rd was isolated and prepared by authors from Korean ginseng radix (*P. ginseng*)	Anti-oxidative effect[a]. Prevented free-oxygen radicals from attacking cell membranes (Yokozawa et al., 1998).	 Rd ($C_{48}H_{82}O_{18}$)

Table 3 (*Continued*)

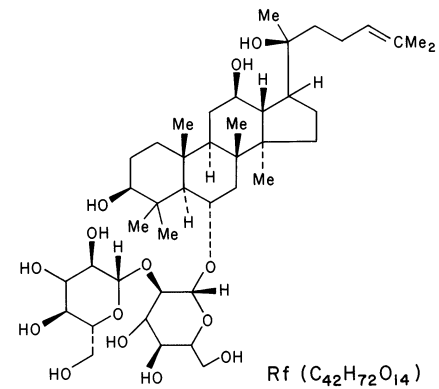
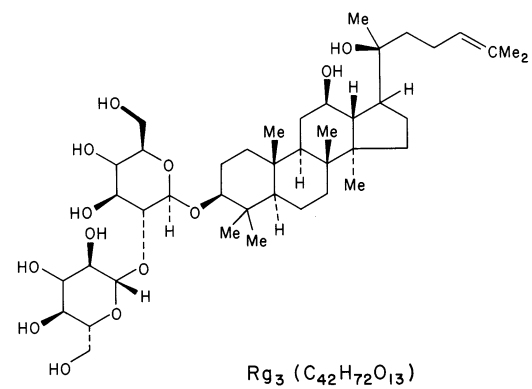
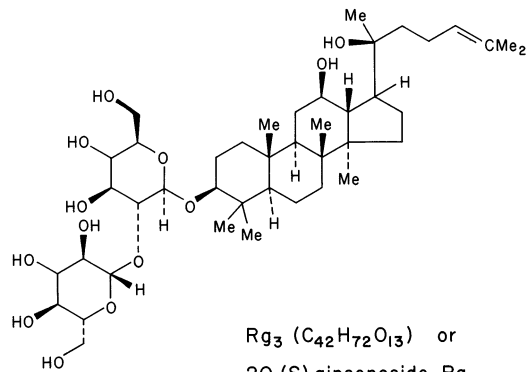
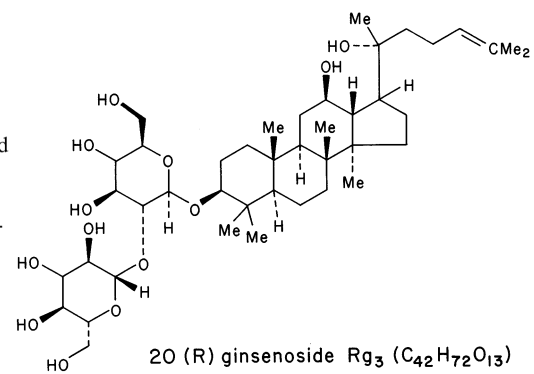
Chemical constituent	Botanical source (family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structures
Ginsenoside Rf	Not specified	Inhibited tonic pain in mice[d] (Mogil et al., 1998)	 Rf ($C_{42}H_{72}O_{14}$)
Ginsenoside Rg_3	*P. ginseng* (Araliaceae)	Inhibited secretion of catecholamine from acetylcholine-stimulated cells (Tachikawa et al., 1997)	 Rg_3 ($C_{42}H_{72}O_{13}$)

Table 3 (*Continued*)

Chemical constituent	Botanical source (family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structures
20(S)- and 20(R)- ginsenosides Rg_3*	Red ginseng was supplied from the Korea Ginseng and Tobacco Research Institute, Tajeon, Korea	Anti-inflammatory effect[e]. The ginsenosides showed receptor binding antagonist activity against Platelet Activating Factor (a lipoprotein) (Jung et al., 1998)	 Rg_3 ($C_{42}H_{72}O_{13}$) or 20 (S) ginsenoside Rg_3
PPD (protopanaxadiol the aglycon of Rh_2)	Purified Rh_2 and its aglycon provided by Dr I Kitagawa, Osaka University, Osaka, Japan	Anti-cancer effect[f]. PPD > Rh_2 inhibited growth of B16 melanoma cells at the G1 phase of cell cycle. PPD-treated cells needed shorter time than Rh_2-treated cells. Both Rh_2 and PPD increased melanin production and intracellular adhesion (Ota et al., 1991)	 20 (R) ginsenoside Rg_3 ($C_{42}H_{72}O_{13}$)

See below for Rh_2

Table 3 (*Continued*)

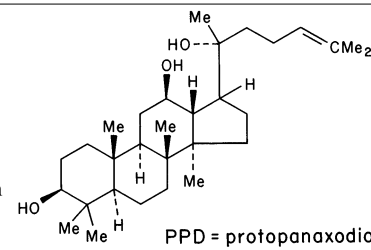
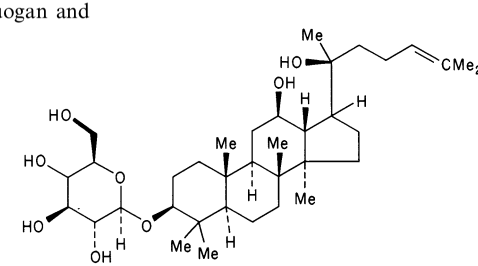
Chemical constituent	Botanical source (family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structures
Ginsenoside Rh_2	Gingseng and Tobacco Research Institute, Tajeon, Korea and Seikanshou Korean Company, Japan	Rh_2 inhibited growth of human ovarian cancer cell lines at 10–60 μM in vitro (best results were observed when Rh_2 was tested in combination with cis-diaminedichloroplatinum (II), CDDP; stimulated programmed cell death (apoptosis) at a dose around IC_{50} (Nakata et al., 1998)	 PPD = protopanaxodiol ($C_{30}H_{52}O_3$)
Ginsenoside Rh_2	Rh_2 was obtained from Dr Shin Il Kim, Korea Ginseng and Tobacco Research Institute, Taejon, Korea	Anti-cancer effect[f]. Promoted apoptosis of human hepatoma SK-HEP-1 cells (Park et al., 1997)	See above for structure
Ginsenoside Rb_1, Rb_4**, Rb_3, Rc, Rg_1, Rg_2, Re, Rh_1	Not specified	Anti-oxidative effecta[a] Decreased the level of free radicals induced by xanthine/xanthine oxidase (Guogan and Yan, 1997)	See above for structures of Rb_1 and Rg_1  Rh_2 ($C_{36}H_{62}O_8$)

Table 3 (*Continued*)

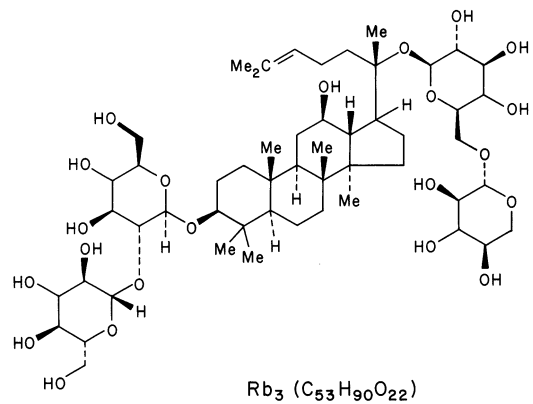
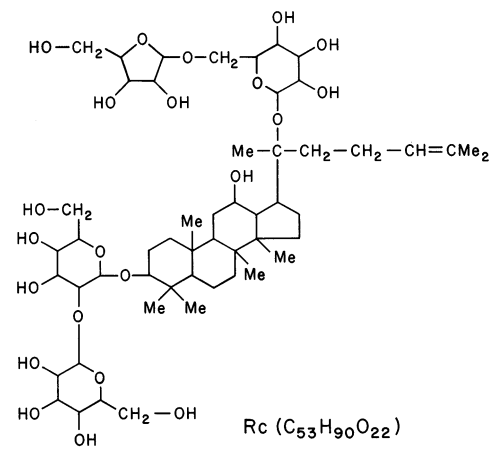
Chemical constituent	Botanical source (family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structures
			 Rb$_3$ ($C_{53}H_{90}O_{22}$)  Rc ($C_{53}H_{90}O_{22}$)

Table 3 (*Continued*)

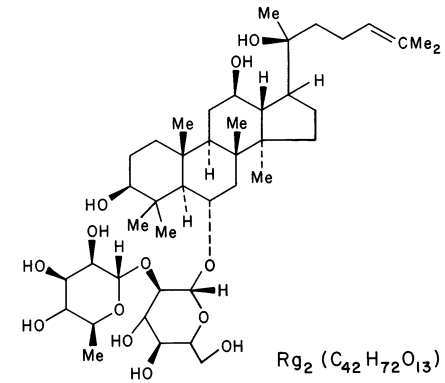
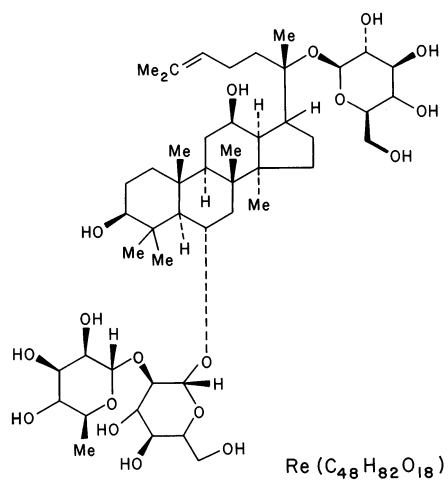
Chemical constituent	Botanical source (family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structures
			 Rg$_2$ ($C_{42}H_{72}O_{13}$)
			 Re ($C_{48}H_{82}O_{18}$)

Table 3 (*Continued*)

Chemical constituent	Botanical source (family based on Wielgorskaya and Takhtajan, 1995) or other/commercial source	Attributed pharmacological activity	Chemical structures
Ginsenosides Rf, Rc, Re, Rg, Rb_1	Korea Ginseng and Tobacco Research Institute, Tajeon, Korea	Anti-stress effect. Order of activity was: $Rf > Rc > Re > Rg_1 > Rb_1$. Ginsenosides inhibited calcium (Ca^{2+}) current and cell membrane capacitance in rat adrenal chromaffin cells. Regenerated catecholamine secretion in adrenal chromaffin cells (Kim et al., 1998c)	See above for structures

* Name of the structure as given by Jung et al., 1998.
** Chemical structure unavailable.
[a] Anti-oxidant.
[b] Anti-impotence effect.
[c] Prevented and treated adverse effects of morphine.
[d] Tonic pain-killer.
[e] Anti-inflammatory.
[f] Anti-cancer agent.

are more potent than those from white ginseng. (No direct comparison in terms of chemistry or amounts of putatively active substances seems to have been done of the components of true ginseng prior to and after processing.)

Although *E. senticosus* and *P. ginseng* are both from the Araliaceae, their chemical composition is very different (cf. Tables 2 and 3). Brekhman (1968) noted and emphasized this long ago. The secondary compounds of *Eleutherococcus* are from different chemical groups such as lignans, saponins, coumarins, vitamins, various sugars and various other even today-unidentified/unnamed compounds. On the other hand, most of the secondary compounds from *Panax* are saponins which, differ from each other by one or a few chemical groups at most. Not only are the chemical compositions of true ginseng and *Eleutherococcus* different, there are differences in their effects on various cultured cell lines (and one might pardonably extrapolate this observation to the human body). From the perspective of their respective chemistries, there seems little basis to use one species as a substitute for another as was initially reported in the early publications of Brekhman and co-workers (see Brekhman 1968, 1976 for comprehensive background bibliographies). True, each of the plants contains anti-oxidants and/or potential anti-cancer compounds, but they differ in a number of other constituents, the pharmacological effects of which do not overlap. True ginseng compounds have been found to have anti-stress activity, to work against male erectile dysfunction (impotence), to kill tonic pain, and even to prevent and treat the adverse effects of morphine (cf. Table 2). The compounds isolated from *Eleutherococcus* include phenylpropanoids (e.g. syringin, caffeic acid, sinapyl alcohol, coniferyl aldehyde), lignans (e.g. sesamin, syringoresinol and its glucoside), saponins (e.g. daucosterol, β-sitosterol, hederasaponin B), coumarins (e.g. isofraxidin and its glucoside), the triterpene betulinic acid, and vitamins (e.g. vitamin E) and provitamins (provitamin A, i.e. β-carotene).

It will be apparent from Table 3 that most of the reportedly active constituents of true ginseng are not only saponins, but they are rather closely related saponins. They share the same cyclopentanoperhydrophenanthrene ring structure, and differ from each other only in their side chains, and rather minimally at that. Even so, the effects of these saponins on various cultured human cell lines are said to be very different. Assertions in the writings of Duke (1989) and Fulder (1980b) and a number of other authors that true ginseng and *Eleutherococcus* have similar activities and thus may be used interchangeably are not supported by any literature citations. Obviously, just because two plants are from the same family and 'look alike' does not mean that they can logically be used as a substitute of one another. The supposed interchangeability between true ginseng and *Eleutherococcus* is a bit reminiscent of those times when the 'doctrine of signatures' or 'similitudes' was used as a guide to nominal pharmacological activity (Court, 1985).

As can be learned from Table 2 each *Eleutherococcus* compound has been shown to have an anti-oxidative effect on more than one tissue or cell type. For example, the lignan syringin displayed a protective effect against X-ray radiation on human leukocytes and thrombocytes. Also, syringin inhibited haemolysis of antibody-coated sheep erythrocytes in guinea pig. The lignan sesamin showed an ability to decrease low density lipoproteins in humans as well as an ability to inhibit activity of cancer promoting 7, 12-dimethylbenz[a]anthracene in mammary cancers in female rats. It also decreased enlarged liver caused by excessive alcohol intake and was able to increase immunoglobulin g levels. The compound β-sitosterol has been shown to have anti-oxidative potential as an inhibitor of human colon cancer (ht-29), and as an anti-inflammatory and antipyretic agent. It also reduced dietary cholesterol absorption in humans and was able to reduce levels of insulin. The coumarin isofraxidin, reported in Table 2, showed cytotoxicity in mice lymphocytic leukemia and stimulated bile as well (i.e. it acted as a choleretic). Caffeic acid has been shown to inhibit xanthine oxidase activity and nitric oxide production, and inhibits the toxic action of aflatoxin from *Aspergillus parasiticus*. Caffeic acid ethyl ester was shown to be a protectant against single stranded DNA breaks in Chi-

nese hamster (v79 cells). Coniferyl aldehyde also showed activity as a protectant against DNA breaks caused by UV-light.

In dramatic contrast to *Eleutherococcus* compounds, the active compounds isolated from true ginseng and listed in Table 3 are all saponins but with rather different pharmacological effects. Most of the active constituents of true ginseng were tested in combinations of two or more, which makes it difficult to establish whether or not each compound has its own pharmacological activity, or only reflects synergistic effects of certain combinations. Rb_1 and Rg_3 have been shown to decrease nitric acid production and have nominally prevented senile decline by the measure of dehydrogenase activity (neuronal viability) and cell integrity by spectrophotometric measurement of LDH (lactic dehydrogenase) in culture medium of neuronal cells. Whereas, Rb_1 and Rg_1 inhibited amphetamine (methamphetamine)-induced hyperactivity and conditioned place preference in mice, Rg_1 alone has been reported to counteract impotence and stimulated copulatory behavior in mice. It also to act as a modulator or even an antagonist of the adverse effects of morphine. By itself, Rg_3 has been shown to inhibit catecholamine secretion by acetylcholine-stimulated cells. Combinations of the 20(S)- and 20(R)-ginsenosides of Rg_3 have been reported as having anti-inflammatory effects by acting as receptor-binding antagonists against platelet activating factor. Rd has been reported as a protector of cell membranes against free oxygen attacks. On the other hand, Rf has been reported as inhibiting tonic pain in mice due to some unexplained process(es). Rh_2 and its aglycon PPD (i.e. protopanaxadiol) have been reported as anti-cancer agents. In particular, Rh_2 was tested on different cancer cell lines and exhibited an anti-cancer effect by selectively promoting programmed cell death –– apoptosis –– of cancer cells. The combination of seven metabolites synthesized in ginseng, Rb_1, Rb_4, Rb_3, Rc, Rg_1, Rg_2, Re, Rh_1, were shown to decrease free radicals induced by xanthine and xanthine oxidase. A qualitative study of five active compounds from true ginseng, Rf, Rc, Re, Rg_1, Rb_1, showed an anti-stress effect on chromaffin-staining adrenal cells.

7. Discussion

7.1. The comparative chemistry and pharmacology of eleutherococcus and true ginseng

7.1.1. Eleutherococcus

Even though we recognized that the historical definition of an adaptogen would be difficult to defend on the basis of rigorous concepts as recognized in western-style medicine, we decided to give the proponents of the term adaptogen the benefit of the doubt. Therefore, we took the approach in our critical analysis of the literature that it might be profitable to seek some hitherto unappreciated or underappreciated avenue that might explain the reported value of adaptogens. Our detailed examination of the relevant literature summarized in Tables 3 and 4 has shown that *E. senticosus* undoubtedly contains constituents that show pharmacological effects when tested in medically accepted tests and assays. Admittedly not all the pharmacological data presented in Table 2, or even most of it, derives from work with *Eleutherococcus*, but there are a number of kinds of compounds in *E. senticosus* that have been studied for their pharmacological action using preparations from other plants, many of them botanically unrelated, that share a common chemistry so far as one or other constituent is concerned. These compounds include phenylpropanoids (e.g. syringin, caffeic acid, sinapyl alcohol, coniferyl aldehyde), lignans (e.g. sesamin, syringoresinol and its glucoside), saponins (e.g. daucosterol, ß-sitosterol, hederasaponin B), coumarins (e.g. isofraxidin and its glucoside), vitamins (e.g. vitamin E) and provitamins (provitamin A, i.e. β-carotene). These molecules have been shown to have a wide range of pharmacological activities, and an associated literature much broader than can be presented here for reasons of space. Six secondary compounds found in *Eleutherococcus* have been shown to have various levels of activity as antioxidants (syringin, caffeic acid, caffeic acid ethyl aldehyde, coniferyl aldehyde), four have been shown to have anti-cancer effects (sesamin, β-sitosterol, isofraxidin), three have been shown to have hypocholesterolemic activities (sesamin, sitosterol, β-sitosterol and β-sitosterol 3-D-glu-

coside), two have been shown to have immunostimulatory activity (sesamin, syringin), one has choleretic activity (isofraxidin) and one had the ability to decrease moderate insulin levels (β-sitosterol and its glucoside), and at least one (syringin) has shown activity as a radioprotectant, one showed anti-inflammatory and antipyretic activities(β-sitosterol) and yet another has shown activity as an antibacterial agent (caffeic acid).

The research cited here using these compounds was carried out using different cell lines as well as on small animals and human subjects. Interestingly, some of them had more than one effect, and although some of the chemical constituents of *Eleutherococcus* are from different chemical classes, some of them show similar pharmacological effects. And, despite the fact that ginseng and *Eleutherococcus* are both in the same family, it is worth re-emphasizing that the secondary compounds of true ginseng are mostly saponins whereas those of *Eleutherococcus* are lignans (syringin, sesamin), saponins (daucosterol, β-sitosterol, hederasaponin B), phenylpropanoids (syringin, caffeic acid, sinapyl alcohol, coniferyl aldehyde), pro-vitamin and vitamin (β-carotene, vitamin E) and coumarins (isofraxidin and its glucoside).

It is well known that reactive oxygen species can damage different systems and cells within these systems and, therefore, may precipitate or cause a number of diseases ranging from such diseases as atherosclerosis, brain and heart ischemia, radiation damage and cancer, to infection and shock and infection (see Gutteridge and Halliwell, 1994; Shahidi, 1997 and refs. cited therein). As shown in Table 2, all active compounds isolated from *Eleutherococcus*, but reported from different botanical sources, had various anti-oxidative effects. (see Sies, 1994 and refs. cited therein as to how anti-oxidant action can be manifested at the clinical level.)

In addition to studies of chemical composition of *Eleutherococcus* plants, cell culture studies by Gui et al. (1991) on multiplication of *Eleutherococcus* via somatic embryogenesis have shown that embryoids developed normally. However, there was no mention of the yield of plant secondary metabolites that might be involved in their production. It would be very interesting indeed if the saponins could be produced in vitro under aseptic culture conditions.

7.2. True ginseng

Once again we emphasize that although *Eleutherococcus* is in the same family as true ginseng, its chemical composition is quite different (Farnsworth et al., 1985; Shibata et al., 1985). We have seen that *Eleutherococcus* contains a fairly large array of secondary compounds such as lignans, triterpenes, vitamins, etc. and that the majority of secondary compounds isolated from true ginseng are saponins. Indeed, as we have already said, many of the effects of *Eleutherococcus* are quite unlike those of true ginseng. Even so, extracts of *Eleutherococcus* do display some effects similar to those of *P. ginseng*. One is the nominal increase in ability to do physical and mental work. Also, the ability to recover more quickly and fully from serious diseases is also attributed to each of the ginsengs (Brekhman, 1968; Mowrey, 1993). Even so, the vast majority of the pharmacological effects of *P. ginseng* are quite different from those from *E. senticosus*. A number of different combinations of true ginseng saponins have been shown to have anti-oxidative, anti-cancer and anti-stress effects in various systems; one saponin (unfortunately, it was not possible for us to match compounds with a 'Rn' from Japanese and Chinese papers with a chemical name, even a trivial one.) Rg_1 has been reported to alleviate male erectile dysfunction, another has been shown to be active in counteracting adverse effects of morphine and yet another has been reported to act as an inhibitor of tonic pain. A combination of these two saponins has been credited as having an anti-inflammatory effect.

According to modern co-evolutionary theory which describes adaptive changes in plant metabolism upon environmental interactions with herbivorous insects (as well as other animals) and the internal needs of each plant as an organism, *Eleutherococcus* and true ginseng synthesize compounds such as those listed in Tables 2 and 3 for their own defensive purposes against external hazards and internal degenerative processes (Fu-

tuyma, 1986). Both plants, *E. senticosus* and *P. ginseng*, have many chemical constituents with a very broad variety and range of pharmacological effects. It seems reasonable to suggest that these multiple or pleurotropic effects are due, in part at least, to synergistic interactions between compounds and their binding to various receptors at the cell surface and inside the cells (see also Sanglier, 1993 for a discussion of immunosuppressants from natural sources and how they might work for additional insights.) Eleutherococcus contains various anti-oxidants and these in turn are also immunostimulants and/or immuno-modulants. Long ago, Braun (1969, 1974, 1977) pointed out similarities in etiology and development of cancers between plants and animals. If one accepts the feasibility of the hypothesis that anti-oxidants may be synthesized by *Eleutherococcus* 'for' self-defense, then it seems reasonable to speculate that the compounds act similarly when mammalian cells encounter (absorb or otherwise bind) these substances (see e.g. Sies, 1994 and refs. cited therein). Some of the secondary metabolites from *Eleutherococcus* reportedly effective pharmacologically are phenolic compounds associated with gallic acid synthesis (Lewis, 1993). And, apparently, they affect mammalian cells in the same way as in their native plant cell environment. Therefore, it is reasonable to suggest that any 'adaptogenic effect' could be explained by an ability of *o*-phenolic glycosides such as coniferin and syringin to be stored in cells and used 'as needed' (Lewis, 1993).

There are number of enzymes, in particular the coniferyl alcohol oxidases, that are responsible for formation of pinoresinol (i.e. syringoresinol), coniferyl alcohol and other coniferyl alcohol derivatives in plants (Lewis, 1993). Any of their antagonists would be responsible for anti-oxidative effects on mammalian cells, say in culture.

It seems reasonably well established that any of the above-mentioned anti-oxidants synthesized and stored in cells of plants like *Eleutherococcus* can be called upon when an oxidative stress to the plant's cell(s) occurs. It is less well established whether the levels of anti-oxidant that are effective in the plant are on the same order or higher in animals. Any given animal organism might require a similar, higher or a lower blood plasma concentration for the same anti-oxidative effect. There are no details that we are aware of pertaining to the metabolism of any of the active constituents from *E. senticosus* in an animal organism, certainly not in humans.

Saponins have been reported as secondary metabolites that prevent or detoxify the effect of various diseases in plants (Osbourn et al., 1998). We have stated that the chemical constituents of true ginseng are saponins with the same basic structure but with different side chains. These different side chains are apparently responsible for bringing about different pharmacological effects. This is probably because they are the active sites of the saponin molecules. Yet they, like the anti-oxidants from *Eleutherococcus*, display synergistic responses in mammalian cell systems (Yamasaki, 1996).

7.3. Adaptogen versus placebo versus panacea?

In order to evaluate the concept of an "adaptogen" by the standards of modern medicine, we compared the term as its main protagonists Lazarev and Brekhman related it to existing pharmacological agents. At the same time, we emphasized that the developers of the adaptogen concept seem not to have determined or specified under which conditions an adaptogen is to be considered being absolutely harmless and innocuous (Brekhman, 1968). In order to so state one obviously would have had to study the effects of a model compound or candidate substance(s), on various systems, its optimal activity, its metabolic degradation and the effects of its products of degradation on an organism.

According to Shapiro and Shapiro (1997), who by contrast carried out extensive studies on placebo effects, a placebo may be defined as follows. "A placebo is any therapy (or that component of any therapy) that is intentionally used for its non-specific, psychological, or psychophysiological therapeutic effect, or that is used for presumed specific therapeutic effect on a patient, symptom, or illness but is without specific activity for the condition being treated…"

"A placebo, when used as a control in experimental studies, is a substance or procedure that is without specific activity for the condition being treated. The placebo effect is the nonspecific psychological or psychophysiological therapeutic effect produced by a placebo" (Shapiro and Shapiro, 1997). Thus it is very clear that the concept of an adaptogen as originally set forth by Lazarev and further developed by Brekhman is very similar to the modern concept of a placebo, which is as 'non-specific' in its effects on an organism as the first one. (For yet another perspective of the 'physiological foundations of the mechanism of action of adaptogens' readers are referred to (Wagner et al., 1994; Wagner, 1995)).

Some have suggested that an 'adaptogen' might be viewed in the context of an immunostimulator that normalizes the immune response of an organism to various stresses (Mowrey, 1993; Rege et al., 1999). This is especially so if one considers an anti-oxidant acting as a protectant against harmful radicals induced by insults from the external environment. Being a protectant as well as having the potential to act synergistically with other antoxidants, an adaptogen could indeed serve to treat or even prevent some diseases, or, in the least, participate in the maintenance of levels of critical substances in the body's fluids etc. (cf. Sies, 1994). This protective activity in turn could help sustain at the clinical level an acceptable level of 'quality of life' in the critically ill such as those with AIDS and other immune deficiency syndromes whose immune system is compromised. In those cases there is a characteristic increased production of free radicals and continuous intake of vitamin E and other immunostimulants is necessary (Peterhans, 1994; Jordao et al., 1998). We have, in fact, been able to find one report in which the claim is made that *Eleutherococcus* synthesizes betulinic acid among many other anti-cancerogenic and anti-oxidative compounds (Zhao et al., 1993). Betulinic acid is a reasonably well-studied compound that has been shown to have anti-cancerogenic and anti-viral effects (Yasukawa et al., 1991; Ma et al., 1999). In particular, betulinic acid has been shown to be effective against HIV 1(human immunodeficiency virus 1) in CEM-4 and MT-4 cell cultures (Vlietinck et al., 1998). On this account, a particular anti-oxidative compound or a combination of compounds could be viewed as offering protection from the effects of harmful radicals from the external environment, as well as exhibiting synergistic effects with other anti-oxidants. In so doing, an 'adaptogen' could prevent some 'new' disease from developing by helping to maintain a certain level of anti-oxidants in the body fluids and thus help sustain quality of life in chronically ill patients.

Even so, the future of anti-oxidants for the moment does not seem to be particularly bright. For example, human clinical trials do not match encouraging findings from in vitro studies. There are a number of reports that β-carotene allegedly prevents cancer. This seems to be somewhat of an exaggeration. There are a number of different kinds of cancer, of course, and clearly the compound is not a panacea. For example, Greenberg and Sporn (1996) found that β-carotene intake increased the risk of lung cancer in the large clinical group studied; it was not able to normalize early stages of a specific gene responsible for neoplastic development! However, in a different study by Giovannucci et al. (1995) the data showed that lycopene or other compounds in fresh tomato and cooked tomato products had a preventive effect against prostate cancer. Also, Franceschi et al. (1994) showed that raw tomato intake is beneficial in lowering risk against cancers of the digestive tract.

The adaptogenic effect of eleutherococcus during and/or after extensive exercise and at high altitude could be explained as the protective antioxidative effect of vitamin E and other anti-oxidants contained in plant extracts. That is to say, under such external 'stresses' there is increased production of oxygen species as the result of compensation to the lack of oxygen in the outside environment (Packer et al., 1994).

Rätsch (1997) claims that *Eleutherococcus* shows an aphrodisiac effect on animals and has suggested that it should have the same "invigorative" and tonic effect on people. In addition to this, Mowrey (1993) speculated that if *Eleutherococcus* can increase stamina in athletes, it might increase sexual performance as well. The last might be true, especially if one could prove that

phenols from *Eleutherococcus* have effects similar or identical to a 'Viagra effect', a situation in which the substance temporarily inhibits nitric oxide as a result of cyclic GMP signal transduction inhibition (Goldstein et al., 1998).

The effect of sesamin, sitosterol and its glucoside, β-sitosterol β-D-glucopyranoside-some compounds with hypocholesteroletic activities-could be explained by their participation in anti-oxidative reactions on LDL (low density lipoproteins), the accumulation of which causes narrowing and eventual closing of vesicles (Moulton et al., 1999). Therefore, we would argue that sesamin, sitosterol and its glucoside can discharge very specific effects at a molecular level. Another perspective on solving the atherosclerosis problem was reported by Moulton et al. (1999). There, angiogenesis (the formation of vesicles) was achieved in atherosclerotic lesions with inhibitors such as TNP-470 and endostatin. Admittedly, more detailed studies are needed to establish the mechanism of a potential endostatin-like inhibition by sesamin, sitosterol and their glucosides.

We have emphasized throughout that compounds from true ginseng have nominally been shown to have various 'adaptogenic' effects. We have seen that true ginseng is widely used as an immune system strengthener in the Eastern Hemisphere. But it is by no means the only plant used for this purpose. Dong Quai (from *Angelica sinsensis*, Apiaceae) is said to be second only to true ginseng in it use as a tonic herb, especially amongst women in China. And, favorite 'tonics' come and go (c.f. Wagner, 1990, 1995; Wagner et al., 1994 for treatment of several other higher plants with reputed 'adaptogenic' activity). Currently there is a fair amount of interest in a 'Polynesian' (actually SE Asian and Australasian) plant with 'remarkable and diverse curative powers', more specifically touted as an ancient Tahitian medicine, Noni (*Morinda citrifolia* L., Rubiaceae). Dixon et al. (1999) have reported that preparations of Noni (usually the fruit 'juice' of *Morinda*) are being used for purposes quite similar to those attributed to true ginseng. Indeed, our detailed study of the literature has verified that true ginseng is reputedly a fortifier of the immune system (Mowrey, 1993), but the evidence in support of this is far from decisive (see e.g. Phillipson and Anderson, 1984; Lewis, 1986; Bahrke and Morgan, 1994 for a critique of some of the studies with true ginseng and the flaws in experimentation).

Clearly the secondary product profile of true ginseng is as complex as that of *Eleutherococcus* and the pharmacology becomes equally complex as a result. Synergistic combination of ginsenosides Rb_1 and Rb_3, as well as the combination of Rb_1 and Rg_1 have been reported to have an anti-oxidative effect on conditions brought about on aging neurons associated increased amounts of nitric acid and, as a result, 'caused' neurodegenerative diseases such as Alzheimer's and Parkinson's (Kim et al., 1998a,d).

It has been suggested that Rg_1 alone had an anti-impotence effect supposedly due to its influence on the cell signaling cascade. Unfortunately, this cascade has not been studied closely yet but its reputation has given true ginseng considerable popularity as a powerful aphrodisiac (Fahim et al., 1982; Yoshimura et al., 1998).

PPD (protopanaxadiol) and Rh_2 supposedly exhibit an anti-cancerogenic effect due to their anti-oxidative mechanism of action in which the cell cycle is blocked at the G1 phase and induces apoptosis (Ota et al., 1991; Park et al., 1997; Nakata et al., 1998). Various other ginsenosides (those with various so-called 'Rns') have also been reported as being anti-oxidants but it is not clear which and at what concentration those ginsenosides might be responsible for the particular effects (Guogan and Yan, 1997; Kim et al., 1998c).

In sum, the anti-oxidative activities of *Eleutherococcus* and true ginseng constituents of the sort reported above might well qualify to be called 'adaptogenic' by some in the sense that they somehow seem to prevent or inhibit undesirable effects of the internal and external environment on/in certain cells and, by extension, on the whole [human] organism. And, it is conceivable but by no means proven that depending on their therapeutic window of activity, some of them might even be so potent that a few doses or even a single dose might decrease cholesterol levels, inhibit

mentally-debilitating processes, or even stop tumors from growing.

One could argue moreover that the activity of a substance may be mono-specific, that is, effective against one particular dysfunction, or poly-specific--that is the effect acts against more than one dysfunction, or beneficial side effects as it were in the western model of a drug. The latter action should not, however, be confused with the effects of panaceas. Panaceas are nominal 'cures' for all or many diseases (from the Greek *pan* or 'all' and *akos* 'cure', that is a *panakeia* or panacea, thus 'cure all or universal remedy'). They are, of course, generally discredited in modern western medicine (Root-Bernstein and Root-Bernstein, 1997). It is possible, of course, that the same compound can be active in the treatment of more than one 'misalignment'. Ibuprofen is but one such example; it acts as an analgesic or painkiller and it is a mild anti-inflammatory agent as well (Reynolds, 1996).

7.4. Problems in the standardization of 'adaptogenic' preparations

A number of field trips to local health food stores and 'natural pharmacies' were made in order to find out the range of preparations of *Eleutherococcus* that might be available (see Tables 4 and 5). From this task we learned that most of the currently available *Eleutherococcus* preparations in the metropolitan New York area (and by extension we presume other areas of the USA) are not standardized or are at best, pseudo-standardized. Even a perfunctory examination of the labels showed that labeling as currently practiced leaves much to be desired. Little of the fastidious 'word-smithing' reflected in the report of the Panel on Definition and Description, (Comple mentary Alternative Medicine Research Methodology Conference) April 1995 on definitions and specific materia medica is in evidence (see O'Connor et al., 1997).

(a) (b)

Fig. 4. Photographs of two attractively packed *Eleutherococcus* preparations available in the USA.

The problems of standardization of plant-derived preparations were addressed early in nineteenth century. Resinous podophyllum (the first use of which was as an emetic) seems to be the first plant-derived material to be concentrated. Prof. John King of the Eclectic Medical Institute, Cincinnati (eclecticism was the precursor of modern alternative medicine so far as herbal products are concerned) is credited with the value of the concentration of plant materials. Podophyllum and many other 'concentrated medicines' were marketed after 1847 and became useful among physicians. Concentrated medicines were more palatable and easier for a physician to carry than other botanicals (Rothstein, 1988).

Directions for use of *Eleutherococcus* preparations are generally very brief, and vary from preparation to preparation depending on the manufacturer (cf. Table 4). Few state how much of the preparation should be taken, when it should be taken (e.g. before, during or after a meal), if there are any contraindications that should be taken into account such as incompatibilities with certain foods, prescription or other medications or certain existing health conditions (e.g. hypertension, diabetes) etc.). Indeed, there is increasing evidence that such contraindications should not be taken as merely incidental (Miller, 1998). And, since the popularity in use of herbal preparations is increasing at a rapid rate, it has been argued that health care providers and other

Table 4
Some commerically-available preparations containing *E. senticosus* or its extractives[a]

Name of preparation	Dosage and directions for use	Country of origin	Reference
Eleu-Kokk/-M Dragees	Not indicated	Germany	Internet: http://www.tee.org/BHSD/bhsd149.html
'*Eleutherococcus curarina*' Tropfen [drops]	Not indicated	Germany	Internet:http://www.tee.org/cgi bin/BHSD-serverseqenum = 49&weiter.x = 47&.y = 29
'Konstitutin Forte' Kapseln [capsules]	Not indicated.	Germany	Internet site as above
40% alcohol 'Extractum *E. senticosii*' (1:1)	(A) Take 2 ml of extract 30 min before meals. (B) Take 29–30 drops as indicated above	CIS (the former USSR)	(A) Sokolov et al., 1990. (B) Mashkovsky, 1988
Standardized[b]. Full Potency™ Siberian Ginseng Root Extract Vegicaps®	Not indicated	New Jersey, USA	Solgar Vitamins and Herb Company, Catalog
Nature's Way. 'Wild Siberian Ginseng Root'	Two or three 410 mg capsules three times a day with water at mealtimes.	Utah, USA	Product label
Enzymatic Therapies®. Siberian Ginseng Extract. Natural herbal extracts standardized to contain >1% eleutheroside E	Take one 100 mg capsule three times a day as an additive to everyday diet.	Wisconsin, USA	Developed in accordance and with recommendations and safety standards by German Commission E. User referred to: Hotline telephone number +1-800-7832286
Natures Herbs®. Power Herbs. Siberian Gingseng	Take two 400 mg capsules 2-3 times a day with water. (100 mg of b and d eleutherosides per capsule)	Utah, USA	Certified Siberian ginseng extract, standardized for a minimum of $B = 400$ mcg, $D = 300$ mcg per capsule in a synergistic base of wild countryside Siberian ginseng. Product label and Internet: http://www.futurebiotics.com
Futurebiotics. Premium Blend Standardized Korean and Siberian Ginsengs	As a dietary supplement for adults. Take one capsule a daily or as directed by a healthcare practitioner. (20% gingsenosides and 0.5% eleutherosides; 500mg/capsule = 300 mg ginsenosides + 200 mg eleutherosides)	New York (Long Island), USA	
Natrol. Four Ginsengs. Guaranteed Potency Extract. A dietary supplement capsules. One capsule contains: *Panax ginseng* extract (32% ginsenosides) 100 mg; Panax quinquefolium (5% ginsenosides) 100 mg; *Eleutherococcus* senticosus extract (8% eleutherosides) 100 mg; Devil's Club = *Oplopanax horridum* (Incorrectly given as *Oplapanax*) 50 mg)	Take One or two capsules twice a day.	Utah, USA	Internet: http://www.natrol.com. and product label
Nature's Herbs®. A Twinlab Co.® Siberian Ginseng Root (404 mg/capsule)	As an additive to the daily diet: 2 to 3 capsules three times a day with a large glass of water.	Utah, USA	Product label

Table 4 (*Continued*)

Name of preparation	Dosage and directions for use	Country of origin	Reference
Fast activities®. Nature's Way. Wild Siberian Ginseng Root alcohol extract. Siberian ginseng root extracted in pure grain alcohol (35-45%) and spring water. Contains 14% eleutherosides B and E; 1.4 mg eleutherosides: 1 ml liquid extract.	Shake well before use. Take 2 ml (for adults and $\frac{1}{2}$ adult dosage for children under 12), three times a day for 8 weeks followed by a 2 week break	Utah, U.S.A.	Product label
Zand®. Active Herbal®. Siberian Ginseng Formula for an Active Life Style 4 fl. oz. (118 ml). Contains: extract of Siberian ginseng root, astragalus root, American ginseng root, Codonopsis root, Fo-Ti root [more than likely of *Polyganum multiflorum*], Ginkgo leaf, licorice root. Herbs extracted in purified water, grain alcohol (ethyl alcohol USP) and vegetable glycerine. Contains 20-30% alcohol.	Take one teaspoon (5 ml) three times a day. May be taken as often as six times a day during periods of intense work and prior to athletic competition. Shake well before using.	California, USA	Product label
Galia Herbs Inc.® Fresh Plant Extracts. Wild ginseng supreme, wild American ginseng, wild Russian siberian ginseng in grain alcohol 30-35%. (1 fl. oz.) Average fresh herb strength 1:15.	Suggested use: thirty to forty drops in a small amount of warm water 3-4 times a day between meals.	Massachusetts, USA	Product label
Alvita®. Caffeine Free Siberian Ginseng Tea bags 1.69 oz (48 g)	Place one tea bag in a cup, add no more than 6 oz. of boiling water, steep for three minutes, remove bag, press bag before removing to enhance the flavor. Add honey to sweeten.	Utah, USA	Product label
Fast Activities® Nature's Way®. Wild Siberian ginseng root glycerine extract			Product label
59 ml (2 fl. oz.). Total Spectrum™ Extract. Siberian ginseng root extracted in (kosher) glycerine and spring water. Potency: 500 mg dry root: 1 ml liquid extract. Double maceration.	Shake well, adults 2 ml three times a day for eight weeks followed by a two weeks break; children under 12 take $\frac{1}{2}$ adult dosage. May be added to food or beverage. Refrigerate after opening.	Utah, USA	Product label

[a] The preparations listed here were of course available on the market when the table was prepared. Experience has shown, however, that manufacturers and suppliers and indeed Websites for the whole range of herbal preparations change rather frequently. Thus, the listings do not imply availibility. Moreover, it should be noted that the FDA (Food and Drug Administration of the USA) requires a disclaimer regarding these products to the effect that 'The statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease'. No endorsement or otherwise of any brand is implied or intended.

[b] It is not clear how the preparation is standardized. This preparation, as well as others sold by this company, is said to represent a standardized exact and powdered raw material of plant roots. Solgar makes the claim that the plant is prepared so 'the result is a potent, premium-quality traditional herbal extract with all of the synergistic and beneficial qualities found in nature'. Finally, it is worth mentioning that *E. senticosus* used to be sold in the USSR in the form of a popular non-alcoholic drink 'Bodrost', and also as an ingredient in one brand of vodka.

Table 5
Some commercially available preparations containing *Panax gingseng* or its extractives[a]

Name of preparation	Dosage and directions for use	Country of origin	Reference
Tinctur Ginsengii[a]	15–20 drops 3 times a day before meals	CIS	Sokolov et al. (1990)
Tablets or powder of Panax ginseng	0.15–0.3 g three times a day before meals	Same as above	Same as above.
Standardized. Full Potency Korean™ Ginseng Root Extract Vegicaps®	No dosage or directions for use indicated	New Jersey, USA	Solgar Vitamins and Herb Company, Catalog
Nature's Herbs. Korean Ginseng Root (556 mg/capsule) contains countryside Korean white ginseng root in a preservative capsule	Take three capsules a day with a large glass of water	Utah, USA	Product label
Nature's Herbs® Power-Herbs® Korean ginseng power-herb® (7% ginsenosides, 100 mg extract/capsule; 530 mg capsule)	As an additive to diet. Adults: one capsule twice a day with a large glass of water	Utah, USA	Product label
Enzymatic Therapy® Panax ginseng extract capsules. Korean ginseng root extract, 100 mg standardized to contain 7% saponins calculated as ginsenoside Rg_1	Take one-two capsules a day as an additive to the everyday diet.	Wisconsin, USA	Product label
Organic Natural. Pacific Brand. The Queen of Herbs in Orient Korean Ginseng for tea (648 mg/capsule, 10 grains)	As beverage: take two capsules each time after meals or as directed	USA	Product label
Zand®. Premium Standard™ Chineses gingseng (25 g). Contains Panax gingseng, distilled water, grain alcohol (ethyl alcohol USP 40–45%). Extract contains 10.3 mg of ginsenosides/ml	Suggested use: shake well, dilute 0.5–1.5 ml in a cup of liquid, 2–3 times a day or as needed	California, USA	Product label
Alvita®. Caffeine free Panax gingseng tea bags 42 g	Take one tea bag in a cup and add no more than 6 oz of boiling water, steep for 3 min, remove bag, press bag before removing to enhance the flavour. Add honey to sweeten	Utah, USA	Product label

[a] It is worth mentioning that many preparations available in the USA seem not to have detailed dosage indications unlike their counterparts from Britain, CIS, Germany, etc.

medical personnel should feel obligated, even if they are not legally mandated, to advise the public on proper use of such medicines (Zink and Chaffin, 1998).

The 103rd Congress, 2d Session (US Congress, 1994) provided guidelines for dietary supplements. However, our Table 4 clearly shows that at the time of completion of this manuscript, labels of preparations that are available to a customer are indeed often very attractive (see Fig. 4 a, b as two randomly selected examples. But labelling remains for the most part general and detailed information on use may be lacking. In many cases, the chemical nature and quantity of purportedly 'active' ingredient(s) are missing. In short, standardisation, if any, appears minimal. Potential users would be hard pressed, we would argue, to make a rational selection. True ginseng preparations are not much better (cf. Table 5).

It is not uncommon among users of various medications not only to take a drug whenever there is a 'problem' but equally often to take more

of it than otherwise might be indicated or prescribed, since there is the widespread perception that if something 'works' at a low dose level, then it should work better still if a higher dose is utilized. Attention has been drawn to this tendency in a slightly different context by Sahelian in his small book "Kava. The Miracle Antianxiety Herb" (Sahelian, 1998). Although a physician, Sahelian encourages users to increase the dosage of their kava intake if a given level seems not to 'work'. By recommending what one might refer to as a personally-determined 'titration' to achieve a desired effect, Sahelian admits that the preparation might not work on a certain individual (cf. Table 6). Of course, this could be due to a number different reasons, such as dosage of a particular drug should be determined according to strength of the preparation, one's body weight, sex, age, peculiarities like attendant chronic diseases which can alter the drug's metabolism, concomitant utilization of other medications etc. Even the ability of the patient's digestive system to degrade a product to liberate bioactive low molecular weight compounds from repeating polymers has been offered as a reason for poor activity in some users (Niwa et al., 1991). In other words, the value of individualized doses has long been recognized in pharmacy and pharmacology. Yet another factor that candidly admits the deplorable state of standardization of many herbal supplements is that one has to even take into account whether the stated ingredients really are reflected by the contents of the marketed product. For instance, the amount of ginsenosides disclosed upon analysis of various ginsengs and ginseng preparations have been shown to vary tremendously (cf. e.g. Liberti and DerMarderosian, 1978; Ziglar, 1979; Lui and Staba, 1980).

Table 6
Inter-individual differences in drug responses[a]

Contributing factors	Comments
Psychological individuality	
Poor compliance with drug therapy	Tailoring of the dosage schedule, drug education
Placebo effects	
Biochemical individuality	
True individual differences in:-	Genetic and environmental factors contribute to the variability
First-pass metabolism	
Systemic clearance	
Renal excretion	
Spontaneous fluctuation in symptoms and disease	Difficult to predict and evaluate in the individual case
Receptor variability	Must be explored under controlled kinetic conditions
Disease-mediated changes in pharmacokinetics	
Kidney disease	Impaired renal excretion of drugs and metabolites; the creatinine clearance satisfactorily predicts this impairment.
Cardiovascular disease	
Age-Dependent Individuality	Impaired renal excretion of drugs in the elderly is well documented

[a] From Sjöqvist (1985). Used with permission of Lippincott Williams & Wilkins (Raven Press), Philadelphia, PA

8. Conclusions

Eleutherococcus senticosus gained considerable advocacy and use among a fairly broad sweep of the Soviet population after its introduction to the general Soviet medical community by the researchers in Siberia. Significantly, it never gained very wide popularity outside the Soviet bloc or sphere of influence. In the West it has usually been characterized (incorrectly to be sure) as a weaker, much less effective substitute for true ginseng (Fulder, 1980b; Tyler, 1994). Some reasons for the apparent lack of wider appreciation of *Eleutherococcus* may be mentioned. First of all, virtually all of the early work on *Eleutherococcus* was published in foreign journals and scholarly monographs and books, mostly in Russian, some in German and Chinese and few in Ukrainian. Lack of ready access to this primary literature or ability of many medical scientists or chemists to read it certainly has served as a deterrent to those in other countries who might have advocated its use or undertaken independent studies on the plant. The general unavailability, more accurately the perceived lack of a reliable supply, of *Eleutherococcus* because of its growth in areas like the

eastern Soviet Union, especially Sakhalin, and the People's Republic of China, must have also played a role in discouraging potential, more mainstream scientists, especially western investigators from getting involved. We have seen that most of the studies of the effects of *Eleutherococcus* preparations on human subjects, along with experiments on animals, were made by Brekhman et al. in the 1960s to the 80s in the former USSR. And, Russian scientists in the 1950s to the 60s also carried out much of the isolation of active compounds from both *Eleutherococcus* and true ginseng. Later, additional chemical work on the isolation of various constituents and studies on their chemistry were done by German (cf. e.g. Wagner et al., 1982; von Wagner et al., 1984), Chinese (cf. e.g. Fang et al., 1985) and Japanese scientists (cf. e.g. Hikino et al., 1986).

As to the relative lack of enthusiasm in the development of *Eleutherococcus* as a western-style pharmaceutical or drug preparation, one can say the following. Of course, different approaches exist around the world as to the process of approval of certain substances from plants intended for medicinal use (Lawson and Bauer, 1998). This fact has also served to exacerbate any existing scientific cultural information gap between development and use of pharmaceuticals in different countries, and this must be construed as another factor in the failure of *Eleutherococcus* to be studied by more workers in the West. Indeed, the substantial financial support required for carrying out laboratory studies, and the fairly long lead-time required for even the chemical work with plants is a real issue. At the clinical level, most experiments utilizing plants suggest that it requires a fairly long time (weeks, months) for the pharmacological effects to become manifest. This is understandable if one takes into account that the levels of secondary constituents are usually not very high, at least in those plants that do not show extreme toxicity. (Parenthetically, some Russian scientists *did* seek to ascertain when optimal levels of the active constituents in crude *Eleutherococcus* were produced by testing material throughout the year and showed that the highest concentrations of eleutherosides were to be found in the spring- and fall-harvested material. However, of greatest concern to them were only the lignans, specifically eleutherosides B, D and E (syringin, (+) and (−) syringoresinol, respectively, Lapchik and Ovodov, 1969). It would be very useful to quantify the production of these and other potentially useful secondary metabolites mentioned in this paper as has begun to been done in the case of *Sesamum indicum* L. (sesame) (Ogasawara et al., 1998). Likewise the intermediary metabolism of the substances in the producer plants therefore needs to be studied. Such knowledge could be very useful in understanding how new drugs could be developed that are more finely tuned to the needs of a given patient (cf. Table 6). Simultaneously, it must be recognized that the proportions of the diverse constituents present in botanical medicines might have a major role in determining efficacy and even safety. It could end up that if proportionality is altered significantly, over-consumption of any given component(s) could lead to lack of activity, altered activity or even toxicity. Incomplete information suggests that caution must be exercised. Indeed, preparations hitherto thought to be safe may turn out to be unsafe if concentrated preparations are used, or even genetically engineered specimens are generated with the nominal desire to increase production of the 'active' metabolite(s).

Biosynthesis of ginsenosides (true ginseng saponins) by cultured cells of *P. ginseng* has been reported. However, the decomposition of ginsenosides apparently gets activated periodically and cleavage occurs leaving carbohydrate residues. For this reason, the amount of ginsenosides may vary in different parts of the plant as well as in different organelles and compartments of different cells of the same plant (Konstantinova et al., 1995).

All the above emphasizes that in the modern, highly competitive scientific world of pharmaceutical research, it seems to be unappealing to invest time and money in activities where fairly quick results are not obtainable. (See Grabley and Thiericke, 1999 for an in-depth treatment of various new strategies and approaches aimed at facilitating natural drug discovery.) Or, as some have suggested, the potential for patent rights is not patently assured (cf. e.g. Patel, 1998; Frieden, 1999 for a 'pro' view and Barrett, 1998 for a 'con' position on this feature of natural products patents).

Despite all the above, and with the full benefit of retrospection, the 'adaptogen concept' and the concept of 'adaptogenic' substances as originally espoused by the Soviets seems not to be the best (or even an appropriate) medico-scientific context for assessing, quantifying and promulgating the virtues of the pharmacological activity or medicinal potential of *Eleutherococcus*, or of any other plant for that matter. Also, it is important to recognize that the reporting of results from studies on eleutherococcus chemistry were often as confusing and imperfect as the erection of the 'adaptogen' concept. Nevertheless, as imperfect and incomplete as the adaptogen concept and the (bio)chemistry underlying it have been, and still are, it has been possible for us to pull out of the literature a number of very interesting and seemingly valid reports where more than one active compound present in *Eleutherococcus* has been tested alone or in combinations that can yield important, indeed, novel, synergistic responses, some of which have been carefully documented in the peer-reviewed literature.

Since specific combinations of synergistically acting substances produce a particular pharmacological effect, it follows that those molecules having the synergistic effects must participate in several reactions. We are quick to re-emphasize that there is a large complex of chemical components in *Eleutherococcus* and with it, comes the inherently high potential for bringing about interactions, potentiations and/or combinatorial responses. These complex responses have been very inadequately studied and will probably not be easy to sort out (Nies and Spielberg, 1996). Admittedly the literature that reports such a wide array of seemingly unrelated pharmacological responses often gives the impression that the studies have been superficial and incomplete and often have the ring of testimonials attesting to panacea-like effects. Last, but not least, it is clear that the inability to provide a distinctive, scientifically unassailable definition of an adaptogen seems to have caused many practitioners of 'conventional' or 'allopathic' western medicine to dismiss the adaptogenic concept as symbolic of 'fringe medical practice' so often characterized by use of disreputable 'nostrums'. (Incidentally, the same may be said of homeopathic medicines Kollerstrom, 1982; Morowitz, 1982).

We hope that as a result of our analysis of the literature that one can now better appreciate the kinds and range of physiological and pharmacological effects of *Eleutherococcus* (and true ginseng, *P. ginseng*). We believe that along with the phytochemical work, although admittedly still relatively incomplete, the results reported to date allow us to conclude that adaptogens, whether so designated or not (and we definitely suggest they not be so designated) have the potential to work against various forms of 'illness').

We have tried to identify and address the problems associated with adaptogens and have attempted to provide a more precise context for understanding them better. We believe that the phytochemical profile, i.e. the presence of various chemical constituents in *E. senticosus* and their demonstrated pharmacological action in a wide range of tests, suggests that one can advocate without reservation further research into this plant. Only by this means will their potential maximal value be substantiated (or discredited) and their worth as models for development of still more effective medicines be taken advantage of. It is certainly more than a little suggestive that many, if not most, of the substances extant as secondary metabolites in plants such as *Eleutherococcus* and true ginseng bear strong resemblance to products that are productions of human metabolism. For example, attention may be drawn to the similarity of substances like saponins and cholesterol, lignans and nucleosides. Might these phytochemicals not be legitimately viewed as molecular analogs of various compounds regularly produced in the course of human anabolism and catabolism? One could speculate still further by pointing out that compounds like AZT and acyclovir are nucleoside analogs, as is syringin. Incorporation into DNA could prevent DNA damage from radiation; the hypocholesterolemic effect of sesamin could be due to a direct effect on de novo cholesterol synthesis; the anti-cancer effect of sesamin, as well as coniferyl aldehyde and caffeic acid ester could likewise be due to incorporation into DNA; the detoxifying effect of sesamin on ethanol could well be due to its effect

on its solubility. The anti-inflammatory effect of sitosterol could be due to an effect much like that of aspirin on prostaglandin. The hypocholesteremic effect of sitosterol might well be due to a mimicking of cholesterol's structure and further inhibition of cholesterol metabolism in the human. And, the anti-hyperglycemic action of sitosterol and its glucoside could be explained by its competitive inhibition of enzyme in glucose breakdown. There is no end to the possibilities. We believe what we have presented on *Eleutherococcus* (and true ginseng as well) is robust and relatively complete. But we readily admit that this analysis is only a point of departure for more focused research.

Last, but not least, in addition to recommending that the terms adaptogen or adaptogenic activity be dropped and replaced with more limited, precise descriptors that can be defended scientifically, we believe that it would be helpful if the designation 'Siberian ginseng' be dropped in favor of the more accurate (and adverse-connotation or baggage-free) designation of *Eleutherococcus*. The two plants *P. ginseng* and *E. senticosus* have far less in common than has hitherto been implied or supposed both in terms of the chemistry of their secondary products and their pharmacological activities.

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