

A Comprehensive Review on Possible Synergistic Therapeutic Effects and Comparison Between Phytochemical and Nutritional Profile of *Medicago sativa* and *Panax ginseng*

Pharmacognosy Magazine

19(4) 799–810, 2023

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DOI: 10.1177/09731296231197306

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Sachin Kumar¹ , Ashok Kumar¹ , Suhasini Nayal², Aman Shukla¹ and Shashank Kailkhura¹

Abstract

Medicago sativa is the “Father of all herbs” or “King of Herbs,” and *Panax ginseng* is the “Man root” or “Herb for all healings.” Individually, both have copious numbers of phytochemicals and nutrients like flavonoids, saponins, ginsenosides, vitamins, minerals, protein, and so on, and this has already been proven by many scientific studies. This comprehensive review aims to provide an overview of the potential health benefits of *M. sativa* and *P. ginseng* as herbs for complete wellness. The review also compares the nutritional profiles of these two herbs and discusses the potential synergistic effects of combining them with some existing scientific evidence. The review highlights the need for further research to validate the efficacy of these herbs as a magical combination for complete wellness and recommends precautions for potential side effects and dosage considerations. Several studies suggest that individually, each herb has various similar clinical significances, like immunomodulating properties, anti-inflammatory properties, antioxidant properties, improved cognitive function, and so on. But in combination, they may show synergistic effects like improved energy and endurance, immune boosters, and cognitive functions. After studying various articles, it is fair to say that both herbs may be considered complete health tonics for complete wellness. Due to limitations and gaps in the current scientific literature, the findings of this review may contribute to further clinical trials and validation of these herbs for improved wellness.

Keywords

Medicago sativa, *Panax ginseng*, synergistic effects, compatibility, potential side effects

Received 08 April 2023; accepted 19 July 2023

Introduction

In contemporary society, medicinal plants are essential since they provide a healthy, sustainable way of life. These plants offer a rich source of therapeutic chemicals, which are increasingly in demand as people look for alternatives to synthetic pharmaceuticals. Their value comes from their capacity to treat a wide range of illnesses with the fewest possible side effects. From traditional remedies to modern herbal medicine, medicinal plants offer a comprehensive approach to well-being, improving both physical and mental health. *Medicago sativa* and *Panax ginseng* are two potent medicinal plants with a long history of use. *M. sativa*, also known as the “father of all medicinal plants,” has been valued for centuries for its numerous health benefits (Putnam &

Orloff, 2014). Its leaves are renowned for being nutrient-dense in vitamins, minerals, and antioxidants, boosting good cholesterol levels, and supporting general well-being (Al-Snafi et al., 2021). *P. ginseng*, commonly referred to as Asian ginseng, is renowned for its adaptogenic properties. It has been used in traditional medicine to fight fatigue, improve

¹Department of Pharmacy, Graphic Era Hill University, Clement Town, Dehradun, Uttarakhand, India

²Department of Pharmacy, JBIT College of Pharmacy, Shankarpur, Uttarakhand, India

Corresponding author:

Sachin Kumar, Department of Pharmacy, Graphic Era Hill University, Bell Road, Clement Town, Dehradun, Uttarakhand 248002, India.

E-mail: srai24304@gmail.com



cognitive function, and foster physical endurance. Additionally, it is also believed to strengthen the immune system, reduce stress, and improve overall vitality. The ginsenoside content of *P. ginseng*, which functions as a natural stimulant and supports numerous biological systems, is thought to be responsible for the herb's therapeutic properties (Lee et al., 2019; Mehta et al., 2021). *M. sativa* and *P. ginseng* are two examples of traditional medicine's profound wisdom, providing holistic solutions for optimal wellness. The main purpose of this comprehensive review is to provide an in-depth analysis of the potential health benefits of *M. sativa* and *P. ginseng* as nature's gift for improved wellness. The review aims to discuss the individual benefits of these herbs as well as explore the potential synergistic effects of combining them. The scope of the review includes a detailed examination of the phytochemical composition of both herbs, their traditional use in herbal medicine, and the most recent scientific evidence on their health benefits. Additionally, the review will discuss potential side effects, interactions with medications, and recommendations for safe and effective use. Overall, the review intends to provide a comprehensive and evidence-based understanding of *M. sativa* and *P. ginseng* as complete fitness and wellness providers, informing and guiding future research, clinical practice, and consumer choices.

While both *M. sativa* and *P. ginseng* are generally considered safe when consumed in moderate amounts, it is important to note that they may have potential side effects or interactions with certain medications. These precautions, side effects, and interactions will be further discussed in this review article. Overall, the potential health benefits of these herbs as complete health tonics provide an attractive option

for those seeking natural remedies to improve overall wellness.

Medicago sativa

M. sativa, commonly known as alfalfa or lucerne, is a forage crop and perennial flowering plant that belongs to the legume family (Lee & Kim, 2014). *M. sativa* is believed to be native to Central Asia and the Middle East. It has been cultivated for thousands of years and has been introduced to many other parts of the world, including Europe, Africa, and the Americas. Today, it is widely cultivated as a forage crop for livestock feed, as well as for its medicinal properties and as a source of food for humans (Al-Snafi et al., 2021). *M. sativa* is rich in vitamins and minerals, including vitamin K, vitamin C, calcium, and magnesium. It also contains flavonoids and saponins, which have anti-inflammatory, antioxidant, and antidiabetic properties. As a health tonic, *M. sativa* has been found to potentially improve digestion, boost immunity, and reduce cholesterol levels (Bartram, 2013; Sharma, 2011). The pharmacological significance of *M. sativa* has been diagrammatically represented in Figure 1.

Phytochemicals and Nutritional Profile

In terms of its nutritional profile, *M. sativa* is a rich source of vitamins, minerals, amino acids, and antioxidants (Jones, 2023). It is particularly high in vitamin K, vitamin C, and folate. It also contains significant amounts of magnesium, potassium, calcium, and iron. Additionally, *M. sativa* is a good source of

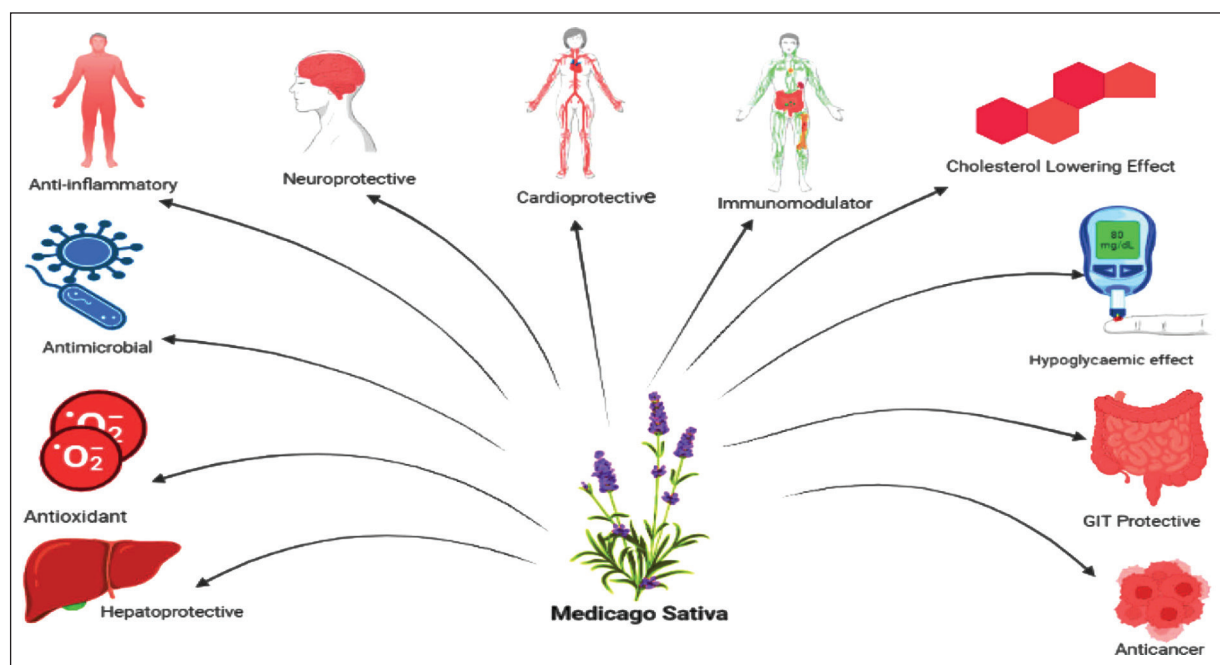


Figure 1. Description of Pharmacological Significances of *Medicago sativa*.

dietary fibers, plant-based protein, and phytochemicals such as flavonoids, isoflavonoids, saponins, lignin, phytoestrogens like coumestrol, alkaloids, some phenolic compounds, and so on (Bora & Sharma, 2011b; Khaleel et al., 2005; Xie et al., 2019). One of the unique characteristics of *M. sativa* is its high chlorophyll content. Chlorophyll is a green pigment found in plants that is thought to have antioxidant and anti-inflammatory properties. *M. sativa* is also a source of other beneficial compounds such as coumestrol, which has been shown to have anticancer properties, and saponins, which may have

cholesterol-lowering effects (Al-Snafi et al., 2021; Bora & Sharma, 2011b; Raeeszadeh et al., 2022). It is important to note that the nutritional and phytochemical composition of *M. sativa* can vary depending on factors such as growing conditions, processing, and storage. Overall, *M. sativa* is a nutrient-dense herb that provides a range of health-promoting compounds. Its nutritional profile makes it a valuable addition to a healthy diet and a potential ingredient in health tonics. All the phytochemicals and nutritional composition with their amounts per 100 g of *M. sativa* are provided in Tables 1 and 2, respectively.

Table 1. Phytochemical Profile of *Medicago sativa* with their Clinical Significance.

Class/Name of Phytochemicals with their Amount and Uses			
Sl.No.	Phytochemicals	Amount per 100 g of <i>M. sativa</i>	Pharmacological Significance
1	Saponins	33.3 mg	Cholesterol-lowering effect, hypoglycemic effect, anti-inflammatory, antioxidant, etc.
2	Flavonoids/flavones	60.8 g	Cardioprotective potential, antiageing, antimicrobial, antineoplastic immunomodulator, etc.
3	Isoflavones	14.2 mg	Neuroprotective effect, SERMs, used to treat menopausal symptoms (hot flashes, mood swings, vaginal dryness) bone health, etc.
4	Phytoestrogenic compounds/ phytosterols	38 mg	Hypolipidemic, cardioprotective, immune supporter, antioxidant, antimicrobial, etc.
5	Coumarin	10.3 mg	Hepatoprotective, anticancer, antibacterial, anticoagulant, anti-inflammatory, etc.
6	Phenol and phenolic compounds	263–270 mg	GIT protective, anti-inflammatory, antibacterial, anticancer

Abbreviations: SERMs, selective oestrogen receptor modulator; GIT, gastrointestinal tract.

Source: <https://www.fatsecret.com/calories-nutrition/generic/alfalfa-sprouts-raw?portionid=54905&portionamount=100.000;> <https://www.healthbenefitstimes.com/alfalfa/>; <https://www.webmd.com/diet/health-benefits-alfalfa>

Table 2. Nutritional Profile of *Medicago sativa* with their Amount per 100 g of Alfalfa Herb.

Name of Nutrients with their Amount		
Sl. No.	Nutrients	Amount per 100 g of <i>M. sativa</i>
1	Carbohydrate	2.1 g
2	Fibers	1.9 g
3	Fat	0.7 g
4	Proteins	4.0–4.5 g
5	Vitamin C	8.2 mg
6	Vitamin K	30 µg
7	Vitamin A	27 IU
8	Folate	36 µg
9	Calcium	32 mg
10	Magnesium	27 mg
11	Potassium	79 mg
12	Iron	0.96 mg
13	Phosphorus	70 mg
14	Zinc	0.92 mg
15	Pyridoxine B6	0.1 mg
16	Riboflavin B2	0.126 mg
17	Pantothenic acid B5	0.563 mg

Source: <https://www.fatsecret.com/calories-nutrition/generic/alfalfa-sprouts-raw?portionid=54905&portionamount=100.000;> <https://www.healthbenefitstimes.com/alfalfa/>; <https://www.webmd.com/diet/health-benefits-alfalfa>.

Potential Health Benefits of *M. sativa*

Cholesterol-lowering Properties

M. sativa, contains saponins that have the potential to lower cholesterol levels (Dixit & Jain, 1990; Mölgaard et al., 1987). A scientific study was published in a book called Indian Medicinal Plants, published by Springer-Verlag Berlin, clearly states that *M. sativa* has been reported to prevent hypercholesterolemia, triglyceridemia, and atherosclerosis in animal subjects (cholesterol-fed rabbit and cynomolgus monkey) and also states that saponin present in alfalfa decreases cholesterol absorption by the intestine in the rabbit. *M. sativa* is rich in dietary fiber, including soluble fiber. Soluble fiber can bind to cholesterol in the digestive system, preventing its absorption and facilitating its excretion from the body (Kelley et al., 1992; Khare, 2007). Saponins present in *M. sativa* can inhibit cholesterol synthesis in the liver and increase the excretion of bile acids, which are involved in cholesterol metabolism (Oakenfull, 2020).

Antioxidant Effects

M. sativa is also rich in antioxidants, including vitamins C and E and flavonoids. These compounds have been shown to neutralize free radicals in the body, reducing oxidative stress and protecting against cell damage that can contribute to chronic diseases (Al-Dosari, 2012; Xie et al., 2008; Zagórska-Dziok et al., 2020). *M. sativa* shows antioxidant effects by scavenging free radicals, inhibiting lipid peroxidation, and chelating metal ions, as well stimulating the activity of various endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (Boldaji et al., 2012; Raeeszadeh et al., 2022).

Anti-inflammatory Potential

M. sativa may have anti-inflammatory properties as well. In a study published in the Journal of Integrative Medicine, an extract of alfalfa was found to reduce inflammation in rat models. This suggests that *M. sativa* may have the potential as a natural remedy for inflammatory conditions in humans as well (Seddighfar et al., 2020). Phytochemicals like saponin and flavonoids in *M. sativa* inhibit the production and activity of pro-inflammatory mediators. These compounds can interfere with the synthesis of inflammatory molecules like prostaglandins, leukotrienes, and cytokines, which are involved in the initiation and progression of inflammatory responses. Also, *M. sativa* has been found to modulate various signaling pathways involved in inflammation, such as nuclear factor-kappa B and mitogen-activated protein kinase pathways (Wang et al., 2019). These pathways play crucial roles in regulating the expression of inflammatory genes and the production of inflammatory mediators. By interfering

with these pathways, *M. sativa* can attenuate the inflammatory response (Choi et al., 2013; Wang et al., 2019).

Immune-boosting Properties

M. sativa contains a range of vitamins and minerals, including vitamins A, C, and E, as well as zinc, iron, and calcium. These nutrients are essential for immune function and may help to boost overall immune health (Rafińska et al., 2017).

It is also reported that *M. sativa* has a cerebroprotective effect against ischemia and reperfusion insults (Bora & Sharma, 2011a). And it also has cardioprotective potential due to its hypolipidemic effect (Dixit & Jain, 1990).

Panax ginseng

P. ginseng, commonly known as Asian ginseng, Chinese ginseng, or Korean ginseng, is also a perennial plant that belongs to the Araliaceae family (Ratan et al., 2021). *P. ginseng* is native to China, Korea, and Siberia and has been used for centuries in traditional medicine (Mehta et al., 2021). Ginseng is a very researched herb; there is a copious amount of data available in the Journal of Ginseng Research and other journals. It is widely recognized for its potential health benefits, including improving energy levels, cognitive function, and immune system function (Lee & Kim, 2014). The pharmacological significance of *P. ginseng* has been diagrammatically represented in Figure 2.

Phytochemicals and Nutritional Profile

P. ginseng contains copious numbers of phytochemicals like ginsenosides, polysaccharides, flavonoids, and so on. Ginsenosides are the main chemical constituent of *P. ginseng* and exhibit antioxidant, anti-inflammatory, and even anticancer potential. Polysaccharides and flavonoids present in ginseng exhibit immunomodulating properties and may help to protect against oxidative stress (Kim, 2018; Mehta et al., 2021). In terms of its phytochemical and nutritional profile, *P. ginseng* is rich in vitamins and minerals like vitamins B₁, B₂, B₁₂ and calcium, iron, potassium, and so on (Kang & Kim, 2016; Kim et al., 2018; Lee, et al., 2019; Lee & Kim, 2014; Mehta et al., 2021).

It is important to note that the phytochemical and nutritional composition of *P. ginseng* can vary depending on factors such as growing conditions, processing, and storage. All the phytochemicals and nutritional composition with their amounts per 100 g of *P. ginseng* are provided in Tables 3 and 4, respectively.

Potential Health Benefits of *P. ginseng*

P. ginseng is a popular health tonic known for its ability to improve overall health and well-being. Here is an overview of some of the potential health benefits of *P. ginseng*.

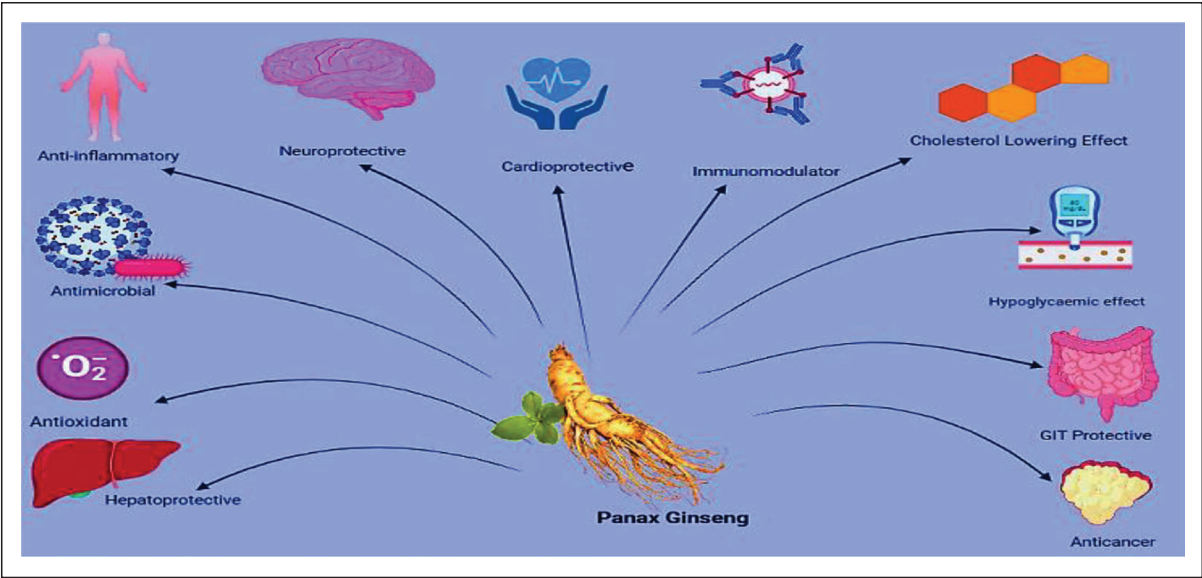


Figure 2. Description of Pharmacological Significances of *Panax ginseng*.

Table 3. Phytochemical Profile of *Panax ginseng* with their Clinical Significance.

Class/Name of Phytochemicals with their Amount and Uses			
Sl. No.	Phytochemicals	Amount per 100 g of <i>P. ginseng</i>	Pharmacological Significance
1	Ginsenosides (main constituents)	8%–10%	Immune supporter, improve cognitive functions, focus, and memory, useful to treat Alzheimer’s, Parkinson’s, and ADHD, anti-inflammatory, hypoglycemic potential, stress removal, cardioprotective, neuroprotector, and even anticancer.
2	Triterpenoids	6–8 g	Immune booster (support the production of WBCs), anti-inflammatory, improve cognitive functions, regulate blood sugar level, cardiovascular supporter, etc.
3	Sugar/Polysaccharides	20–25 g	Regulate blood sugar, immunomodulator, cognitive functions, cardioprotector, etc.
4	Phenols/Phenolic Compounds	0.5–1 g	Antioxidant, cardioprotector, regulate blood sugar, etc.
5	Flavones/Flavonoids	0.1–0.5 g	Antioxidant, reduce oxidative stress, cardioprotector, lower cholesterol level, antimicrobial, etc.

Abbreviations: ADHD, attention deficit hyperactivity disorder; WBCs, white blood cells.

Source: <https://herbalsupplements.health/plant/ginseng-red>; <https://www.verywellhealth.com/the-benefits-of-ginseng-89219>

Boosts Immunity

P. ginseng has immune-boosting properties that can help improve the body’s natural defense system against infections and diseases. Studies have shown that ginseng can enhance the production of immune cells and increase the activity of natural killer cells, which are responsible for fighting off viruses and harmful bacteria (You et al., 2022).

Improves Cognitive Function

P. ginseng has been shown to improve cognitive function, including memory, attention, and focus. It is believed that ginsenosides, the active compounds in ginseng, help protect brain cells from damage, improve blood flow to the brain, and enhance neurotransmitter activity, resulting in improved cognitive function (Barnes et al., 2007; Khare, 2007).

Table 4. Nutritional Profile of *Panax ginseng* with their Amount per 100 g of *P. ginseng* Herb.

Name of Nutrients with their Amount		
Sl.No.	Nutrients	Amount per 100 g of <i>P. ginseng</i>
1	Carbohydrate	18 g
2	Fibers	3 g
3	Proteins	2.0 g
4	Fat	0.6 g
5	Vitamin C	0.9 µg
6	Thiamine B1	0.5 mg
7	Riboflavin B2	0.1 mg
8	Niacin B3	1.2 mg
9	Pantothenic Acid B5	0.5 mg
10	Pyridoxine B6	1 mg
11	Folic Acid B9	37 µg
12	Calcium	27 mg
13	Iron	1.5 mg
14	Phosphorus	131 mg
15	Potassium	704 mg
16	Sodium	13 mg
17	Zinc	0.9 mg
18	Magnesium	28 mg

Source: <https://herbalsupplements.health/plant/ginseng-red>; <https://www.verywellhealth.com/the-benefits-of-ginseng-89219>.

Reduces Stress and Fatigue

P. ginseng has adaptogenic properties, which means it can help the body cope with stress and fatigue. Studies have shown that ginseng can help reduce stress levels, improve mood, and increase energy levels, making it a popular choice for people looking to boost their mental and physical performance (Hyun et al., 2022; Ratan, et al., 2021).

Enhances Physical Performance

P. ginseng has been shown to improve physical performance by increasing oxygen uptake and reducing fatigue. Studies have found that ginseng can increase endurance, improve recovery time, and reduce muscle damage following intense exercise (You et al., 2022; Kim et al., 2018).

Regulates Blood Sugar Levels

P. ginseng has been shown to help regulate blood sugar levels, making it a potentially useful herb for people with diabetes. Studies have found that ginseng can improve insulin sensitivity, reduce blood sugar levels, and lower the risk of complications associated with diabetes (Coon & Ernst, 2002; Kim, 2018). Oxidative stress can contribute to the development of insulin resistance and impaired glucose metabolism. *P. ginseng* possesses antioxidant properties, which can help

reduce oxidative stress and potentially improve blood sugar control (El-Khayat et al., 2011; Lee & Kim, 2014).

In a study, it was also found that *P. ginseng* reduces oxidative stress and acts as a cardioprotector (Hyun et al., 2022; Kim, 2018).

Overall, *P. ginseng* is a promising health tonic that offers a wide range of potential health benefits, including boosting immunity, improving cognitive function, reducing stress and fatigue, enhancing physical performance, and regulating blood sugar levels.

Comparisons Between the Phytochemical and Nutritional Profile of *M. sativa* and *P. ginseng*

M. sativa, also known as alfalfa, is a plant that is commonly used as feed for livestock. It is also consumed by humans as a source of nutrients. *P. ginseng*, on the other hand, is a medicinal herb that is used for its health benefits. Here is the comparison between the nutritional profiles of these two plants based on the presence of macronutrients, vitamins, and minerals (Barnes et al., 2007; Boon & Smith, 2004; Khare, 2007; Mehta et al., 2021).

In terms of phytochemicals, both herbs contain unique phytochemicals, as *M. sativa* contains flavones, isoflavones, phenolic compounds, saponin, and so on, whereas *P. ginseng* contains ginsenosides as its main constituents and also

contains flavonoids, polysaccharides, phenolic compounds, triterpenoids, and so on. Both have different phytochemicals, but various clinical significances are similar in both herbs, like antioxidant, anti-inflammatory, immune booster, cardio protector, and so on.

If the comparison is on the subject of macronutrients, then both have copious numbers of macromolecules like proteins, fibers, carbohydrates, amino acids, and so on. The presence of these macronutrients makes them an energy booster, endurance promoter, and immunomodulator.

Concerning the presence of vitamins, both have abundant numbers of vitamins. But *M. sativa* contains more vitamin C than ginseng. *M. sativa* is a good source of vitamin K, whereas vitamin K is not present in ginseng. So, *M. sativa* is richer in vitamins than ginseng.

In terms of minerals, *M. sativa* and *P. ginseng* are both excellent sources of minerals, but when we compare them, we can say that in the case of some minerals, *M. sativa* is richer than *P. ginseng*, and in the case of others, ginseng is richer than alfalfa. But both are good sources of minerals. A comparison between the phytochemical and nutritional profiles of *M. sativa* and *P. ginseng* has been graphically represented in Figures 3 and 4.

While both *M. sativa* and *P. ginseng* are good sources of nutrients and contain beneficial phytochemicals, they have different nutritional profiles. *M. sativa* is higher in protein and fiber, as well as vitamins K and C, while *P. ginseng* is higher in potassium, magnesium, and ginsenosides.

Discussion on Potential Synergistic Effects

However, there is limited evidence or studies to prove that *M. sativa* in combination with *P. ginseng* exhibits a synergistic effect, but there is also no evidence to prove that both of them interact negatively when used together. Various products are already available on the market in the form of syrup, malt, and so on, that contain alfalfa and ginseng as primary ingredients (Omeo Alfalfa with Ginseng, SBL Alfalfa Malt, Dr Reckeweg Alfalfa Tonic, Schwabe's Alfalfa Tonic are some of these products). Several studies suggest that, individually, each herb has various similar clinical significances, like immunomodulating properties, anti-inflammatory properties, antioxidant properties, improved cognitive function, and so on.

Improved Energy and Endurance

Individually, both herbs improve physical performance, aerobic capacity, and cognitive functions. *P. ginseng* helps to enhance aerobic capacity and exercise performance in healthy individuals, and it is usually administered by gym freaks, athletes, sports persons, and various health-conscious individuals (Scaglione et al., 2005; Shergis et al., 2012). On the other side, *M. sativa* helps to boost exercise endurance and reduce the level of lactate and fatigue in individuals (Barnes et al., 2007; Page, 1997). Due to their similar effects on physical performance, there is no doubt that the

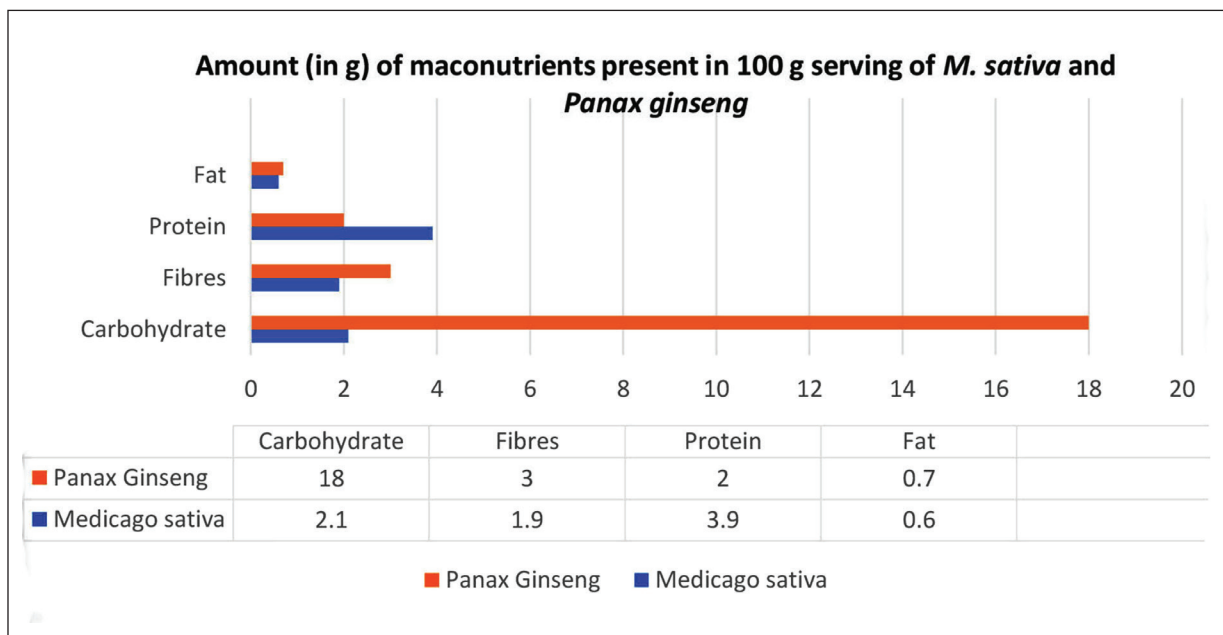


Figure 3. Comparative Description of the Quantity of Macronutrients Present in 100 g Serving of *Medicago sativa* and *Panax ginseng*.

Source: <https://www.fatsecret.com/calories-nutrition/generic/alfalfa-sprouts-raw?portionid=54905&portionamount=100.000>; <https://www.healthbenefitstimes.com/alfalfa/>; <https://www.webmd.com/diet/health-benefits-alfalfa>.

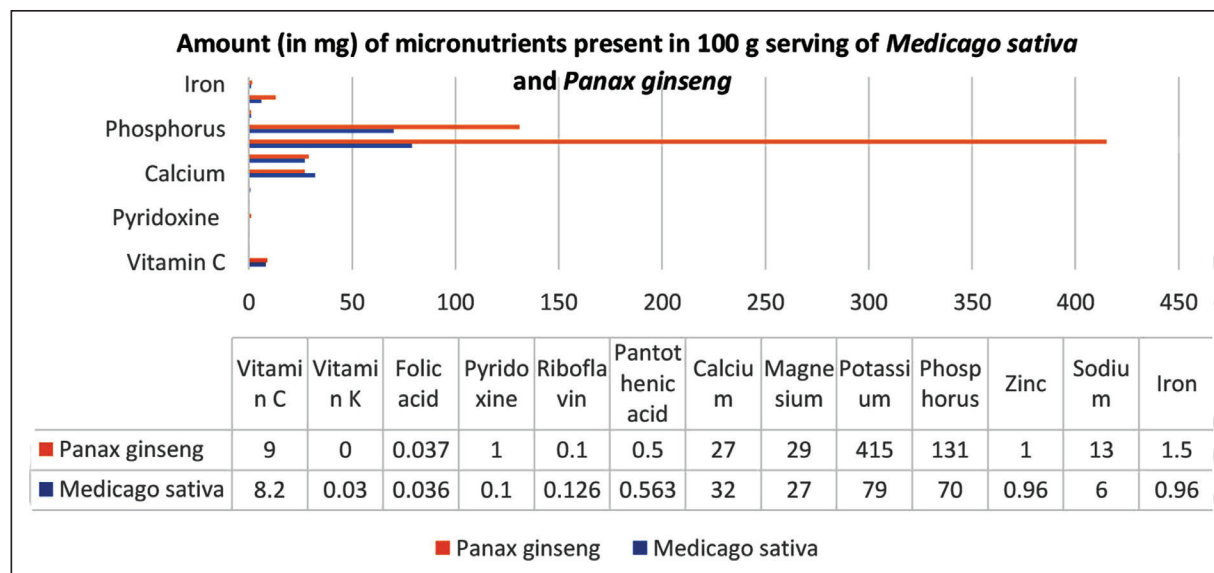


Figure 4. Comparative Description of the Quantity of Micronutrients Present in 100 g Serving of *Medicago sativa* and *Panax ginseng*.

Source: <https://herbalsupplements.health/plant/ginseng-red>; <https://www.verywellhealth.com/the-benefits-of-ginseng-89219>.

combination of *M. sativa* and *P. ginseng* may enhance their effects on energy and endurance, potentially leading to improved physical performance.

Immune Support

M. sativa contains a range of antioxidants, including vitamins C and E, beta-carotene, and flavonoids, which can help to reduce inflammation and protect against oxidative damage (Al-Dosari, 2012; Raeeszadeh et al., 2022).

P. ginseng has also been shown to have immune-boosting effects. A few studies have been published in the Journal of Ginseng Research that found that *P. ginseng* supplementation improved immune function in healthy individuals (Kang & Min, 2012; Ratan et al., 2021). Combining *M. sativa* and *P. ginseng* may enhance their antioxidant and immune-boosting effects, potentially improving overall health and reducing the risk of chronic diseases.

Cognitive Function

M. sativa contains various phytochemicals like triterpene, saponin, choline, and so on, which are essential for brain function, including memory and cognitive processing (Bora & Sharma, 2011; Liu et al., 2019). A study published in the Journal of Food Biochemistry found that triterpene saponin found in *M. sativa* has a potential effect on the treatment of neurodegenerative diseases (Liu et al., 2019). *P. ginseng* has also been shown to improve cognitive function (Geng et al., 2010; Khare, 2007). A study published in Translational and

Clinical Pharmacology found that *P. ginseng* supplementation improved cognitive performance in healthy adults as well as in individuals with cognitive impairment (Park et al., 2019). Combining *M. sativa* and *P. ginseng* may enhance their cognitive benefits, potentially improving mental clarity, focus, and memory retention.

In conclusion, while there is limited research specifically examining the potential synergistic effects of combining *M. sativa* and *P. ginseng*, there is scientific evidence to support the individual health benefits of each plant, which may suggest potential synergistic effects. However, it is important to consult with a healthcare professional before adding any new supplements or herbs to your health regimen, especially if you have any underlying health conditions or are taking medications.

Possible Side Effects, Precautions, and Interaction with Medications

The potential side effects of *M. sativa* and *P. ginseng* vary depending on the individual and the dose taken. Here are some of the most common side effects associated with these supplements:

Side Effects Associated with *M. sativa*

M. sativa herb should be avoided in cases of lupus because it has been reported that *M. sativa* can induce Systemic lupus erythematosus (SLE) like syndrome in a model of female monkey (Barnes et al., 2007; Malinow et al., 1981a). This

type of side effect is associated with the presence of Canavanine, which is a structural analog to the amino acid arginine and a non-protein amino acid (Alcocer-Varela et al., 1985; Boon & Smith, 2004). *M. sativa* seed contains approximately 8.33 to 13.6 mg/kg of canavanine, and this amount is enough to be toxic to all species of animals due to the reduction or blocking of the binding of amino acids to their respective enzymes and their incorporation into proteins (Barnes et al., 2007).

There has been reported a condition called Pancytopenia in those who were taking *M. sativa* seed up to 80–160 g/day for cholesterol-lowering purposes (Malinow et al., 1981a).

There are some other side effects of *M. sativa*, such as photosensitivity (sunburn or any other skin reactions), digestive upset (bloating, mild dysentery, or diarrhea), and hypoglycemic effects.

Precautions

M. sativa herb or seed should not be used during pregnancy or lactation (Brinker & Stodart, 2001). Also avoid those who have any history of lupus or any family history of SLE (Barnes et al., 2007; Boon & Smith, 2004; Brinker & Stodart, 2001).

Side Effects Associated with *P. ginseng*

Scientific evidence related to the side effects of *P. ginseng* has been published in the Acta Psychiatrica Scandinavica Journal, which states that intake of *P. ginseng* may lead to manic symptoms. In this study, the author suggested that patients with an antidepressant condition should avoid ginseng administration because it can produce manic symptoms like insomnia, overstimulation, and so on (Vázquez & Agüera-Ortiz, 2002).

Various clinical trials have suggested that there are several side effects related to ginseng that are similar to those with placebo. The most commonly reported side effects are headaches, insomnia, and gastrointestinal tract-related disorders (Coon & Ernst, 2002).

In any case of gender or age, there are some case studies that have reported that potential side effects associated with *P. ginseng* are uterine bleeding, prolonged QT syndrome, gynecomastia, unwanted elevation in blood pressure, acute lobular hepatitis, and bradycardia during atrial fibrillation (Kim et al., 2008; Paik & Lee, 2015; Ratan et al., 2021; Seo et al., 2017).

Precautions

P. ginseng should not be taken by an individual who is nervous, tensed, hysteric, maniacal, or epileptic/schizophrenic (Kim et al., 2008).

Interactions with Medications

M. sativa may interact with certain medications, and it is important to speak with a healthcare professional before taking these supplements if you are taking any medications. Here are some of the potential interactions to be aware of: blood thinners, hormone replacement therapy, contraceptive medications (birth control pills), and antidiabetic medications (Barnes et al., 2007; Boon & Smith, 2004; Brinker & Stodart, 2001).

P. ginseng may also interact with some medications, and it is important to consult with a healthcare professional before using ginseng if you are on any therapy. Here are some medications that can interact with ginseng: anticoagulants like warfarin, antidiabetic drugs like metformin, and antihypertensive drugs (Cheng, 2005; Choi & Song, 2019).

Conclusion

M. sativa (alfalfa) and *P. ginseng* (ginseng) are two popular herbal supplements that have been traditionally used as complete health tonics. These supplements contain bioactive compounds that have been studied for their potential health benefits.

One of the potential benefits of *M. sativa* is its high nutrient content, including vitamins A, C, E, and K, as well as minerals like calcium, magnesium, and potassium. *M. sativa* may also contain bioactive compounds that offer antioxidant and anti-inflammatory effects, which may protect against chronic diseases such as heart disease and cancer.

P. ginseng, on the other hand, has been shown to improve cognitive function and may offer benefits for mental health. Studies suggest that ginseng may help improve focus, memory, and overall cognitive performance. *P. ginseng* may also offer benefits for the immune system, potentially helping to reduce the risk of infections and illnesses.

While both *M. sativa* and *P. ginseng* offer potential health benefits, it is important to note that they should not be used as a substitute for medical treatment. It is also crucial to speak with a healthcare professional before taking these supplements, especially if you have any underlying health conditions or are taking medication.

In summary, with proper usage and guidance, *M. sativa* and *P. ginseng* can be valuable additions to a healthy lifestyle and a well-balanced diet. Their potential benefits make them promising candidates for further research and exploration in the field of natural health and wellness.

Discussion of the Limitations and Gaps in the Current Scientific Literature

While there is some scientific literature on the potential health benefits of *M. sativa* and *P. ginseng*, there are also limitations and gaps in the current research that need to be addressed.

One limitation is the lack of standardization in the preparation and dosing of these supplements. The bioactive compounds in these supplements can vary widely depending on factors such as the species of plant used, the part of the plant used, and the method of preparation. This makes it difficult to compare results across studies and establish consistent dosing guidelines.

Another limitation is the relatively small number of human studies that have been conducted on these supplements. While there is some evidence to suggest that alfalfa and ginseng may offer potential health benefits, many of the studies have been conducted on animals or *in vitro*. More human studies are needed to better understand the effects of these supplements on human health and establish safe and effective dosages.

There are also gaps in the literature when it comes to the long-term safety of these supplements. While *M. sativa* and *P. ginseng* are generally considered safe when taken in recommended dosages, more research is needed to determine the potential risks of long-term use. This is especially important for people with underlying health conditions or who are taking medications that may interact with these supplements.

In conclusion, while there is some scientific literature on the potential health benefits of *M. sativa* and *P. ginseng*, there are also limitations and gaps in the current research that need to be addressed. Further research is needed to better understand the effects of these supplements on human health, establish consistent dosing guidelines, and determine their long-term safety.

Recommendations for Future Research and Clinical Trials

Based on the limitations and gaps in the current scientific literature on *M. sativa* and *P. ginseng*, there are several recommendations for future research and clinical trials.

Standardization of preparation and dosing: There is a need for standardized methods for the preparation and dosing of these supplements. This will help to ensure consistency across studies and enable more accurate comparisons of results.

Large-scale human studies: More large-scale human studies are needed to determine the potential health benefits of these supplements in humans. These studies should be well-designed, randomized, and placebo-controlled and should include diverse populations.

Long-term safety studies: While these supplements are generally considered safe, more research is needed to determine their long-term safety. This is especially important for people with underlying health conditions or who are taking medications that may interact with these supplements.

Mechanistic studies: Further research is needed to better understand the mechanisms of action of these supplements. This will help to identify the specific bioactive compounds

responsible for their potential health benefits and how they work in the body.

Clinical trials for specific health conditions: There is a need for clinical trials to determine the efficacy of these supplements for specific health conditions, such as cognitive decline, immune system disorders, and inflammation.

Interactions with medications: Further research is needed to determine the potential interactions between these supplements and medications, especially for people who are taking multiple medications.

Finally, further research and clinical trials are needed to better understand the potential health benefits and risks of *M. sativa* and *P. ginseng*. Addressing the limitations and gaps in the current literature through standardization, large-scale human studies, long-term safety studies, mechanistic studies, clinical trials for specific health conditions, and interactions with medications will help to establish the safety and efficacy of these supplements for human health.

Abbreviations

M. sativa: *Medicago sativa*; *P. ginseng*: *Panax ginseng*; SERMs: selective oestrogen receptor modulator; GIT: gastrointestinal tract; IU: International unit; ADHD: attention deficit hyperactivity disorder; WBCs: white blood cells; SOD: superoxide dismutase; NF-Kb: nuclear factor-kappa B; MAPK: mitogen-activated protein kinase pathways.

Acknowledgments

The authors are thankful to their parents and the Dean and Director, School of Pharmacy, Graphic Era Hill University, Dehradun for providing support, guidance and valuable data.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

ORCID iDs

Sachin Kumar  <https://orcid.org/0000-0002-4249-1819>

Ashok Kumar  <https://orcid.org/0000-0002-4625-1089>

References

- Alcocer-Varela, J., Iglesias, A., Llorente, L., & Alarcón-Segovia, D. (1985). Effects of l-canavanine on T cells may explain the induction of systemic lupus erythematosus by alfalfa. *Arthritis and Rheumatism*, 28(1), 52–57. <https://doi.org/10.1002/art.1780280109>
- Al-Dosari, M.S. (2012). *In vitro* and *in vivo* antioxidant activity of alfalfa (*Medicago sativa* L.) on carbon tetrachloride intoxicated

- rats. *American Journal of Chinese Medicine*, 40(4), 779–793. <https://doi.org/10.1142/S0192415X12500589>
- Al-Snafi, A.E., Khadem, H.S., Al-Saedy, H.A., Alqahtani, A.M., Batiha, G.E.-S. & Abolfazl, J.-S. (2021). A review on *Medicago sativa*: A potential medicinal plant. *International Journal of Biological and Pharmaceutical Sciences Archive*, 1(2), 22–33. <https://doi.org/10.30574/ijbpsa.2021.1.2.0302>
- Barnes, J., Anderson, L.A., & Phillipson, J.D. (2007). *Herbal medicines* (3rd ed.). Pharmaceutical Press.
- Bartram, T. (2013). *Bartram's encyclopedia of herbal medicine*. Hachette UK.
- Boldaji, S.A.H., Khavari-Nejad, R.A., Sajedi, R.H., Fahimi, H., & Saadatmand, S. (2012). Water availability effects on antioxidant enzyme activities, lipid peroxidation, and reducing sugar contents of alfalfa (*Medicago sativa* L.). *Acta Physiologiae Plantarum*, 34(3), 1177–1186. <https://doi.org/10.1007/s11738-011-0914-6>
- Boon, H., & Smith, M. (2004). *The complete natural medicine guide to the 50 most common medicinal herbs* (2nd ed.). Robert Rose.
- Bora, K.S., & Sharma, A. (2011a). Evaluation of antioxidant and cerebroprotective effect of *Medicago sativa* Linn against ischemia and reperfusion insult. *Evidence-Based Complementary and Alternative Medicine: eCAM*, 2011, 792167. <https://doi.org/10.1093/ecam/nea019>
- Bora, K.S., & Sharma, A. (2011b). Phytochemical and pharmacological potential of *Medicago sativa*: A review. *Pharmaceutical Biology*, 49(2), 211–220. <https://doi.org/10.3109/13880209.2010.504732>
- Brinker, F.J., & Stodart, N. (2001). *Herb contraindications and drug interactions* (3rd ed.). Eclectic Publishing Medical.
- Cheng, T.O. (2005). Ginseng and other herbal medicines that interact with warfarin. *International Journal of Cardiology*, 104(2), 227. <https://doi.org/10.1016/j.ijcard.2004.07.022>
- Choi, K.C., Hwang, J.M., Bang, S.J., Kim, B.T., Kim, D.H., Chae, M., Lee, S.A., Choi, G.J., Kim, D.H., & Lee, J.C. (2013). Chloroform extract of alfalfa (*Medicago sativa*) inhibits lipopolysaccharide-induced inflammation by downregulating ERK/NF- κ B signaling and cytokine production. *Journal of Medicinal Food*, 16(5), 410–420. <https://doi.org/10.1089/jmf.2012.2679>
- Choi, M.K., & Song, I.S. (2019). Interactions of ginseng with therapeutic drugs. *Archives of Pharmacological Research*, 42(10), 862–878. <https://doi.org/10.1007/s12272-019-01184-3>
- Coon, J.T., & Ernst, E. (2002). *Panax ginseng*: A systematic review of adverse effects and drug interactions. *Drug Safety*, 25(5), 323–344. <https://doi.org/10.2165/00002018-200225050-00003>
- Dixit, V.P., & Jain, P. (1990). Hypolipidemic effects of *Medicago sativa* seed extracts (50%) EtOH in rabbits under experimental conditions. *Ancient Science of Life*, 10(1), 52–55.
- El-Khayat, Z., Hussein, J., Ramzy, T., & Ashour, M. (2011). Antidiabetic antioxidant effect of *Panax ginseng*. *Journal of Medicinal Plants Research*, 5(18), 4616–4620.
- FatSecret (ND). *Calories in 100 g of alfalfa sprouts and nutrition facts*. <https://www.fatsecret.com/calories-nutrition/generic/alfalfa-sprouts-raw?portionid=54905&portionamount=100.000>
- Geng, J., Dong, J., Ni, H., Lee, M.S., Wu, T., Jiang, K., Wang, G., Zhou, A.L., & Malouf, R. (2010). Ginseng for cognition. *Cochrane Database of Systematic Reviews*, 8(12), CD007769. <https://doi.org/10.1002/14651858.CD007769.pub2>
- Herbal Supplements. *Korean red ginseng: Benefits, side-effects, usage, dosage, history, and differences*. <https://herbalsupplements.health/plant/ginseng-red/>
- Hyun, S.H., Bhilare, K.D., In, G., Park, C.-K., & Kim, J.-H. (2022). Effect of *Panax ginseng* and ginsenosides on oxidative stress and cardiovascular diseases: Pharmacological and therapeutic roles. *Journal of Ginseng Research*, 46(1), 33–38. <https://doi.org/10.1016/j.jgr.2021.07.007>
- Jones, T.R.D. (2023). Alfalfa facts, health benefits and nutritional value. *Health Benefits Times*. <https://herbalsupplements.health/plant/ginseng-red/>
- Kang, O.-J., & Kim, J.-S. (2016). Comparison of ginsenoside contents in different parts of Korean ginseng (*panax ginseng* C. A. Meyer). *Preventive Nutrition and Food Science*, 21(4), 389–392. <https://doi.org/10.3746/pnf.2016.21.4.389>
- Kang, S., & Min, H. (2012). Ginseng, the “Immunity Boost”: The effects of *Panax ginseng* on immune System. *Journal of Ginseng Research*, 36(4), 354–368. <https://doi.org/10.5142/jgr.2012.36.4.354>
- Kelley, M.J., Thomas, J.N., & Story, J.A. (1992). Changes in cholesterol accumulation and steroid excretion in response to cellulose, alfalfa or oats in cholesterol-fed rats. *Nutrition Research*, 12(4–5), 509–518. [https://doi.org/10.1016/S0271-5317\(05\)80021-1](https://doi.org/10.1016/S0271-5317(05)80021-1)
- Khaleel, A.E., Gad, M.Z., El-Maraghy, S.A., Hifnaway, M.S., & Abdel-Sattar, E. (2005). Study of hypocholesterolemic and antiatherosclerotic properties of *Medicago sativa* L. cultivated in Egypt. *Journal of Food and Drug Analysis*, 13(3), 212–218.
- Khare, C.P. (2007). *Indian medicinal plants*. Springer.
- Kim, J. H. (2018). Pharmacological and medical applications of *Panax ginseng* and ginsenosides: A review for use in cardiovascular diseases. *Journal of ginseng research*, 42(3), 264–269. <https://doi.org/10.1016/j.jgr.2017.10.004>
- Kim, J.H., et al. (2018). Triterpenoids from panax ginseng and their pharmacological activities. *Molecules*, 23(4), 645. <https://doi.org/10.3390/molecules23040645>
- Kim, K.M., Kwon, H.S., Jeon, S.G., Park, C.H., Sohn, S.W., Kim, D.I., Kim, S.S., Chang, Y.S., Kim, Y.K., Cho, S.H., Min, K.U., & Kim, Y.Y. (2008). Korean ginseng-induced occupational asthma and determination of IgE binding components. *Journal of Korean Medical Science*, 23(2), 232–235. <https://doi.org/10.3346/jkms.2008.23.2.232>
- Lee, C.H., & Kim, J.-H. (2014). A review on the medicinal potentials of ginseng and ginsenosides on cardiovascular diseases. *Journal of Ginseng Research*, 38(3), 161–166. <http://doi.org/10.1016/j.jgr.2014.03.001>
- Lee, J.s., et al. (2019). Antiinflammatory effects of ginsenosides Rg3 and Rh2 in activated microglia and their neuroprotective effects on dopaminergic neurons. *Neurochemistry International*, 90–99. <https://doi.org/10.1016/j.neuint.2019.01.008>
- Liu, X.-G., Lv, M.-C., Huang, M.-Y., Sun, Y.-Q., Gao, P.-Y., & Li, D.-Q. (2019). A network pharmacology study on the triterpene saponins from *Medicago sativa* L. for the treatment of Neurodegenerative diseases. *Journal of Food Biochemistry*, 43(8), e12955. <https://doi.org/10.1111/jfbc.12955>
- Malinow, M.R., Bardana, E.J. JR, & Goodnight, S.H. JR (1981a). Pancytopenia during ingestion of alfalfa seeds. *The Lancet*, 317(8220), 615. [https://doi.org/10.1016/s0140-6736\(81\)92063-8](https://doi.org/10.1016/s0140-6736(81)92063-8)
- Malinow, M.R., McNulty, W.P., McLaughlin, P., Stafford, C., Burns, A.K., Livingston, A.L., & Kohler, G.O. (1981b). The toxicity of alfalfa saponins in rats. *Food and Cosmetics Toxicology*, 19, 443–445. [https://doi.org/10.1016/0015-6264\(81\)90448-x](https://doi.org/10.1016/0015-6264(81)90448-x)

- Mehta, S.D., Rathore, P., & Rai, G. (2021). Ginseng: Pharmacological action and phytochemistry prospective. In: Hano, C., & Chen, J.-T. (Eds.), *Ginseng – Modern aspects of the famed traditional medicine* (pp. 1–15). IntechOpen. <http://doi.org/10.5772/intechopen.99646>
- Mølgaard, J., von Schenck, H., & Olsson, A.G. (1987). Alfalfa seeds lower low density lipoprotein cholesterol and apolipoprotein B concentrations in patients with type II hyperlipoproteinemia. *Atherosclerosis*, 65(1–2), 173–179. [https://doi.org/10.1016/0021-9150\(87\)90019-0](https://doi.org/10.1016/0021-9150(87)90019-0)
- Oakenfull, D. (2020). Saponins in the treatment of hypercholesterolemia. In *Handbook of lipids in human nutrition* (pp. 107–112). CRC Press.
- Page, L.R. (1997). *Renewing male health and energy*. Healthy Healing, Inc.
- Paik, D.J., & Lee, C.H. (2015). Review of cases of patient risk associated with ginseng abuse and misuse. *Journal of Ginseng Research*, 39(2), 89–93. <https://doi.org/10.1016/j.jgr.2014.11.005>
- Park, K.-C., Jin, H., Zheng, R., Kim, S., Lee, S.-E., Kim, B.-H., & Yim, S.-V. (2019). Cognition enhancing effect of panax ginseng in Korean volunteers with mild cognitive impairment: A randomized, double-blind, placebo-controlled clinical trial. *Translational and Clinical Pharmacology*, 27(3), 92–97. <https://doi.org/10.12793/tcp.2019.27.3.92>
- Putnam, D.H., & Orloff, S.B. (2014). *Forage crops. Encyclopedia of agriculture and food systems* (pp. 381–405). <https://doi.org/10.1016/B978-0-444-52512-3.00142-X>
- Raeeszadeh, M., Beheshtipour, J., Jamali, R., & Akbari, A. (2022). The antioxidant properties of alfalfa (*Medicago sativa* L.) and its biochemical, antioxidant, anti-inflammatory, and pathological effects on nicotine-induced oxidative stress in the rat liver. *Oxidative Medicine and Cellular Longevity*, 2022, 2691577. <https://doi.org/10.1155/2022/2691577>
- Raeeszadeh, M., Beheshtipour, J., Jamali, R., & Akbari, A. (2022). The antioxidant properties of alfalfa (*Medicago sativa* L.) and its biochemical, antioxidant, anti-inflammatory, and pathological effects on nicotine-induced oxidative stress in the rat liver. *Oxidative Medicine and Cellular Longevity*, 2022, 2691577. <https://doi.org/10.1155/2022/2691577>
- Rafińska, K., Pomastowski, P., Wrona, O., Górecki, R., & Buszewski, B. (2017). *Medicago sativa* as a source of secondary metabolites for agriculture and pharmaceutical industry. *Phytochemistry Letters*, 20, 520–539. <https://doi.org/10.1016/j.phytol.2016.12.006>
- Ratan, Z.A., Haidere, M.F., Hong, Y.H., Park, S.H., Lee, J.-O., Lee, J., & Cho, J.Y. (2021). Pharmacological potential of ginseng and its major component ginsenosides. *Journal of Ginseng Research*, 45(2), 199–210. <https://doi.org/10.1016/j.jgr.2020.02.004>
- Ratan, Z.A., Youn, S.H., Kwak, Y.-S., Han, C.-K., Haidere, M.F., Kim, J.K., Min, H., Jung, Y.-J., Hosseinzadeh, H., Hyun, S.H., & Cho, J.Y. (2021). Adaptogenic effects of *Panax ginseng* on modulation of immune functions. *Journal of Ginseng Research*, 45(1), 32–40. <https://doi.org/10.1016/j.jgr.2020.09.004>
- Scaglione, F., Pannacci, M., & Petrini, O. (2005). The standardised G115® *Panax ginseng* CA Meyer extract: A review of its properties and usage. *Evidence-Based Integrative Medicine*, 2(4), 195–206. <https://doi.org/10.2165/01197065-200502040-00003>
- Seddighfar, M., Mirghazanfari, S.M., & Dadpay, M. (2020). Analgesic and anti-inflammatory properties of hydroalcoholic extracts of *Malva sylvestris*, *Carum carvi* or *Medicago sativa*, and their combination in a rat model. *Journal of Integrative Medicine*, 18(2), 181–188. <https://doi.org/10.1016/j.joim.2020.02.003>
- Seo, H.W., Suh, J.H., So, S.H., Kyung, J.S., Kim, Y.S., & Han, C.K. (2017). Subacute oral toxicity and bacterial mutagenicity study of Korean Red ginseng oil. *Journal of Ginseng Research*, 41(4), 595–601. <https://doi.org/10.1016/j.jgr.2017.01.009>
- Sharma, K.S. (2011). Phytochemical and pharmacological potential of *Medicago sativa*: A review. *Pharmaceutical Biotechnology*, 211–220. <https://doi.org/10.3109/13880209.2010.504732>
- Shergis, J., Zhang, T., Zhou, W., & Xue, C. (2012). P04. 27. *Panax ginseng* in randomized controlled trials: A systematic review. *BMC Complementary and Alternative Medicine*, 12, 1–1.
- Vázquez, I., & Agüera-Ortiz, L.F. (2002). Herbal products and serious side effects: A case of ginseng-induced manic episode. *Acta Psychiatrica Scandinavica*, 105(1), 76–77. <https://doi.org/10.1034/j.1600-0447.2002.10489.x>
- Wang, L., Xie, Y., Yang, W., Yang, Z., Jiang, S., Zhang, C., & Zhang, G. (2019). Alfalfa polysaccharide prevents H2O2-induced oxidative damage in MEFs by activating MAPK/Nrf2 signaling pathways and suppressing NF-κB signaling pathways. *Scientific Reports*, 9(1), 1782. <https://doi.org/10.1038/s41598-018-38466-7>
- WebMD. (2022). *Health benefits of alfalfa*. <https://www.webmd.com/diet/health-benefits-alfalfa>
- Xie, Y., Wang, L., Sun, H., Wang, Y., Yang, Z., Zhang, G., & Yang, W. (2019). Immunomodulatory, antioxidant and intestinal morphology-regulating activities of alfalfa polysaccharides in mice. *International Journal of Biological Macromolecules*, 133, 1107–1114. <https://doi.org/10.1016/j.ijbiomac.2019.04.144>
- Xie, Z., Huang, J., Xu, X., & Jin, Z. (2008). Antioxidant activity of peptides isolated from alfalfa leaf protein hydrolysate. *Food Chemistry*, 111(2), 370–376. <https://doi.org/10.1016/j.foodchem.2008.03.078>
- You, L., Cha, S., Kim, M.Y., & Cho, J.Y. (2022, November). Ginsenosides are active ingredients in *Panax ginseng* with immunomodulatory properties from cellular to organismal levels. *Journal of Ginseng Research*, 46(6), 711–721. <https://doi.org/10.1016/j.jgr.2021.12.007>
- Zagórska-Dziok, M., Ziemiańska, A., Nizioł-Łukaszewska, Z., & Bujak, T. (2020). Antioxidant activity and cytotoxicity of *Medicago sativa* L. Seeds and Herb extract on skin cells. *BioResearch Open Access*, 9(1), 229–242. <https://doi.org/10.1089/biores.2020.0015>