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Therapeutic profile of fermented ginseng: Future prospective in India

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Abstract
From the very beginning, humans have been searching for medicines to maintain their good health and for the treatment of various diseases. The world's largest population uses drugs produced from natural sources. Ginseng is most studied medicinal herb which has long been traditionally used in Asian countries to treat various diseases. The pharmacological activities of ginseng and its constituent's i.e. ginsenosides are well established.
The conversion of these ginsenosides into smaller compounds through fermentation improves its pharmacological activities, potency and bioavailability. The objective of this article is to summarize the pharmacological activities of fermented ginseng through literature searched from PubMed, PubMed Central, and Google Scholar of articles. To the best of our knowledge, this is the first report for summarization of pharmacological properties of fermented ginseng. In conclusion, it is high time to upgrade the scientific research by adopting various techniques like fermentation to achieve more potent, efficacious and bioavailable drug from the potential herb of Indian origin.

Keywords: Fermentation, ginseng, therapeutic, ginsenosides

Introduction
Many traditional systems of medicine exist all over world for hundreds or even thousands of years. The medicines used in these systems are mostly derived from herbs. Herbal products have lots of potential in the identification and discovery of new drugs [1]. *Panax ginseng* is commonly used traditional medicinal herb belongs to family Araliaceae and used in Asian countries for the management of various diseases. It is one of the most researched medicinal herbs around the world. The primary bioactive constituents of *Panax ginseng* are indeed ginsenosides, which are a class of triterpene saponins [2-8]. It has anti-inflammatory [9-10], anti-allergic [11], anti-diabetic [12, 13-14], anti-oxidation [15] and anti-cancer [16] properties etc. Despite the fact that ginseng is the most research medicinal herb in world, there is lack of sufficient clinical data and studies have been limited to cells and animal models. This may be due to that the ginsenosides have low bioavailability, instability in gastrointestinal tract and high metabolic rate in the body. Therefore, the scientific world has now started to move its efforts to improve the bioavailability of ginsenosides [17]. Most of the traditional systems of medicine working in the world are continuously using new technologies to address the issues with herbal drug preparation, processing, therapeutic efficacy, dosage regulation, safety etc. for drug development. Fermentation is an ideal process of biotransformation of active compounds to more pharmacologically active compounds using microbial enzymes which in turn exhibit more therapeutic potencies and lowers the toxicity of the treated plant. The non-medicinal components, such as proteins, sugars, and other substances are also removed making the herbal drugs more bio-available and safe [18]. In the current review, some of the pharmacological properties of fermented ginseng are being summarized.

Pharmacological activities of fermented ginseng
There have been a large number of *in vitro* and *in vivo* studies investigating the pharmacological effect of ginseng and ginsenosides and its molecular mechanism but due to unavailability of sufficient reliable clinical data, the efficacy of ginseng in human patients has not been clearly established. The ginsenosides present in ginseng are biotransformed into smaller deglycosylated forms using fermentation process and it was found that these deglycosylated forms have more effective pharmacological properties [19-21].

Anti-Oxidative

Anti-oxidants are naturally occurring compounds that can serve as defence against free radicals. The secondary metabolites i.e., polyphenols, flavonoids etc. identified in plants are generally involved in defense against several factors like free radicals, pathogens etc. The concentration of these polyphenols, flavonoids were found greater in fermented red ginseng compared to red ginseng and thus exert more anti oxidative activity [22]. Similarly, red ginseng marc extracts prepared via fermentation using Bacillus subtilis and Saccharomyces cerevisiae showed high level of polyphenols [23]. Similarly, the total phenolic compound content detected in fermented seed extracts by *B. subtilis*, *P. pentosaceus* and *L. gasseri* were higher as compared to non-fermented control group. These results suggested that different fermentation strains produce different total phenolic compound content. The enhanced ABTS radical scavenging and SOD enzyme activity at 100 ppm were detected in the fermented ginseng samples compared to the control group [23]. The ageing and fermentation technique was applied on dried ginseng sprouts and significant changes in the physicochemical qualities and compositional components were obtained in various ginseng sprouts. Significant increases in deglycosylated ginsenosides and antioxidant properties were noted for the ageing and fermentation sources [24].

In vivo study suggested that the administration of fermented ginseng extract can improve the antioxidant status during aging by increasing the activities of SOD, catalase, glutathione peroxidase, glutathione reductase and glutathione-S-transferase [25]. Similarly, the activity of SOD, catalase and glutathione peroxidase was found increased on administration of the fermented red ginseng in Sprague-Dawley rats (Diabetes induced) at concentration of 100 mg/kg compared to diabetes normal and normal control groups. This indicated that fermented red ginseng has greater antioxidant effects [26].

In an another study, the fermented white ginseng exhibited higher SOD activity than the white ginseng attributed may be due to the increased levels of Rg3 ginsenoside from 0.03 mg/g to 1.76 mg/g in fermented white ginseng [27]. Similarly, the SOD and catalase mRNA expression levels were also found upregulated in hydroponic ginseng fermented with *Lactococcus lactis* [28]. *In vitro* experiments using fermented cultured wild ginseng root extract showed antioxidant and neuroprotective properties, as well as inhibiting acetylcholinesterase (AChE) activity at dose of at least 250 mg/kg [29]. The above reported findings indicated that fermentation significantly improved the overall radical scavenging activities of ginseng, which could be explained by the augmented content of antioxidant compounds. Fermentation can alter the phytochemical profile of plant materials, potentially affecting their bioactivity [30].

Anti-diabetic

The anti-diabetic effect of ginseng is well documented. In one of the study, 62.5% decrease in the level of blood glucose and 10.2% increase in glucose tolerance were observed when probiotic fermented red ginseng was orally administered in the diabetes mouse model as compared to non-diabetic mice [31].

Similarly, the administration of fermented ginseng extract in type 2 diabetes mellitus murine model showed that lower levels of blood glucose and significantly higher levels of adiponectin and serum insulin as compared with the control group. Apart from this, higher levels of peroxisome proliferator - activated receptor gamma 2 and glucose transporter protein 2 mRNAs were found in fermented ginseng extract group [32]. The results showed that the fermented ginseng extract exerted anti-diabetic effects in type 2 diabetic mice. Further, In a 4-week trial, the effects of fermented red ginseng supplementation were determined to be limited to lowering glucose readings after an oral glucose tolerance test; no discernible changes in fasting plasma glucose (FPG) were seen [33-34].

The ginsenosides which are known to have anti-diabetic activity are Rb1, Rb2, Rc, Rd and Rg3 are found elevated along with ginsenoside Rh2 in the fermented red ginseng as compared with red ginseng [35]. Results showed that fermented red ginseng extracts significantly reduce blood glucose levels and increase plasma insulin levels in diabetic rats. The mRNA expression of some of the genetic hallmarks of insulin resistance in the liver and in muscle was found increased in the group treated with fermented red ginseng compared with the control group [36]. Similarly, In a four-week long, randomized, double-blind, placebo-controlled clinical trial, the data of 42 healthy participants in meal tolerance test showed that group that received the fermented red ginseng supplementation was significantly reduced the 2-h postprandial glucose level from 9.3 mmol/l to 7.7mmol/l and increased the 2-h postprandial insulin level 39.2 µU/ml to 56.3 µU/ml while no significant difference was observed in placebo group [33]. In study conducted on *ob/ob* mice models with supplementation of fermented ginseng showed decrease in the blood glucose levels due to up regulation of GLUT1 and GLUT 4 transporters results in the more glucose uptake. Significantly decrease in body weight and blood glucose is also observed in *db/db* mice during a 35-day treatment when when treated with 0.5 g/kg fermented steam-dried ginseng berry extracts [2]. In a double blind clinical trial, 93 postmenopausal women were randomly divided and supplemented with fermented red ginseng and placebo for 2 weeks. Significant decrease in glycosylated hemoglobin (HbA1c) and insulin were observed in the fermented red ginseng group compared which may be due to negative effects of aldosterone and increase in the levels of growh hormone, dehydroepiandrosterone sulfate and estradiol [37].

Hepato protective effect

There are several reports on hepatoprotective effect of ginseng. However, the hepatoprotective effect of fermented ginseng is limited. The high level of serum ALT and AST is an indication of liver damage. A study conducted on adult male Sprague-Dawley rats showed the group II animals that were only fed with a high-fat diet with filtered tap water for eight weeks had ALT and AST levels 61.3 U/L and 169.7 U/L respectively. The Group III animals who fed with a high-fat diet with drinking water containing 0.5% fermented red ginseng for eight weeks had ALT and AST levels 45.1 U/L and 141.5 U/L respectively while Group IV animals who fed with a high-fat diet with drinking water containing 1% fermented red ginseng for eight weeks had ALT and AST levels 41.2 U/L and 120.9 U/L respectively [21]. The levels of serum ALT and AST in Group II were higher than in Group III and Group IV. Treatment with fermented red ginseng resulted in a notable decrease in ALT and AST levels compared with those in Group II, indicating that fermented red ginseng exhibits hepatoprotective effects.

There are reports that Compound K protects HepG2 cell cytotoxicity induced by t-BHP. The oral administration of both ginsenoside Rb1 and compound K significantly inhibited the increment of ALT and AST induced by t-BHP in mice [38].

Similarly, rat liver injury caused by paracetamol showed that pretreatment with fermented ginseng, containing compound K at high concentration, attenuated AST and ALT levels in rats. It has been suggested that compound K inhibited the phosphorylation of JNK in HepG2 cells [39]. A study demonstrated by Je showed that extracts of fermented sprouts of ginseng attenuate alcohol or endotoxin-induced acute liver injury in mice. Fermented sprouts of ginseng extracts were given orally to mice one hour prior to an injection of ethanol or lipopolysaccharide and D-galactosamine. To investigate the impact of extracts on reducing hangover symptoms, the latency of the righting reflex was tracked. The findings showed that fermented sprouts of ginseng decreased hepatic necrosis and plasma levels of alanine ALT and AST, enhanced the activity and expression of ethanol-metabolizing enzymes, and dramatically decreased the latency of the righting reflex. The extracts' antioxidant activity caused a decrease in 4-hydroxynonenal levels while increasing cytochrome P450 2E1 expression during the ethanol metabolism. As a result, it was found that Fermentation increased the effectiveness of sprouts of ginseng extracts in alleviating hangovers and attenuating endotoxin-induced acute liver damage [40].

Study conducted to evaluate the cytotoxic effects of fermented black ginseng on the HepG2 cells showed that treatment with 10-200 µg/ml fermented red ginseng inhibited cell viability in a dose-dependent manner and the survival rate of the cells treated with 50 µg/ml of fermented red ginseng was approximately 70% compared to that of the control cells [41].

Anti-inflammatory

Inflammation is a complex biological process triggered by a number of factors such as trauma, microbial infection, or xenobiotic insults that elicit cell injury or death [42]. The inflammation is largely regulated by the activation of NF-κB and the inhibition of this activation NF-κB leads to the anti-inflammatory response. Study conducted by Seong *et al* [20] showed that fermented wild ginseng contains anti-inflammatory activity via NF-κB inactivation. In this study, the RAW264.7 macrophage cell lines were pretreated with fermented wild ginseng followed by stimulation with LPS. Western blot analysis showed that pretreatment with fermented wild ginseng inhibited LPS-induced degradation of IκB-α and phosphorylation of NF-κB. Further investigation showed that RAW264.7 macrophage cell lines pretreated with fermented wild ginseng inhibits the activation of NF-κB signaling in DSS-induced colitis mice. Similar results were also obtained with fermentation extracts consisting of soybean, red ginseng and Citrus Unshiu Peel. In mice induced by lipopolysaccharide, fermented ginseng polysaccharides inhibited increases in liver index, serum AST level, and a few inflammatory-related variables like TNF-α, IL-1β, and IL-6 [43]. In addition, Park *et al*. demonstrated the anti-inflammatory effects of hydroponic ginseng fermented with Bacillus strains. The cellular nitric oxide formation, prostaglandin E2 concentration, and expressions of inflammatory cytokines were reduced in the cells treated with the fermented hydroponic ginseng, and especially Bacillus subtilis KU201 [44]. There are reports fermented red ginseng have more potential to suppress production of nitric oxide in the LPS-stimulated RAW264.7 macrophage cells, than that of red ginseng [45].

Anti- Cancer

Cancer is a group of diseases characterized by cells with uncontrolled growth is a leading cause of death worldwide. Among the minor ginsenosides, Rg3 has been reported as anti-carcinogenic [46]. Rg3 has been found highly increased in a ginseng Extract Fermented with *Phellinus linteus* (GFPL) as compared to ginseng. The different concentrations of GFPL inhibited the growth of human lung carcinoma cell line A549. These data suggest that GFPL may potentially be effective as a lung cancer therapy [47].

It was also found that treatment of human colorectal carcinoma cell line HT-29 with fermented ginseng extract (BST204) increased the number of cells at G1 from 51% to 69%, whereas the cells at S phase decreased from 25% to 12%, indicating that BST204 inhibits cell cycle at G0-G1. BST204 treatment significantly up-regulated the expression of tumor suppressor genes, p53 and Cdk inhibitor, p21WAF1/Cip1, while the protein levels of Cdk2, cyclin E, and cyclin D1, the cyclin-dependent kinase/cyclins involved in G1 or G1/S transition, were down-regulated in a concentration dependent manner [48]. The anti-coronavirus disease-2019 (COVID-19) impact of FBCG was assessed in a Vero E6 cell line that was infected with the coronavirus SARS According to the findings, FBCG not only prevents this virus strain from replicating within the cell but also lowers the quantity of viral RNA copies in the extracellular environment [49].

The above study indicated that fermented ginseng extract with a high concentration of effective ginsenosides enhanced the anti-proliferative activity against human colon cancer cells.

Stronger anti-tumor metastatic activities were also reported in Fermented ginseng Extract than those of ginseng extract [50]. In another study, the prophylactic intraperitoneal administration of fermented red ginseng extract at concentration of 500 µg/ mouse inhibited lung metastasis about 81.1% [26]. The red ginseng extracts fermented by Paecilomyces tenuipes inhibited HCT116 human colon cancer cell proliferation in a dose-dependence manner [51]. The result of the above study demonstrated that the bio transformed ginsenosides in fermented red ginseng increases normal colon cell growth and inhibits the proliferation of human colon cancer cells.

Conclusion & Future Perspectives

The pharmacological properties of ginseng are well established. The active constituents of plant are present in the glycoside forms which are hydrophilic in nature due to glycosyl group which makes them less bioavailable, bioactive and permeable. The fermentation process hydrolyze glycoside to aglycone and make the active constituents more bioactive, bioavailable and permeable. The anti-oxidative, anti-inflammatory, anti-diabetic etc. properties are reported to be increased when fermented form of ginseng was used.

In India, Ayurveda and Unani are the two major traditional system of medicine and scientific studies are being carried out on a large number of Indian herbs in Indian research Institutes, Universities etc. Till date, there is no major development in different forms of the drugs and are being used as they are mentioned in the classical literature. On the other hand, China and Korea has made advancement in promoting its own therapies and drugs like ginseng, gingko etc. with scientific evidence.

Withania somnifera is an Indian medicinal herb used in both Ayurveda and Unani system of medicine and is considered having similar pharmacological properties to ginseng. Its

pharmacological properties are also well described but very limited information is available relating to the fermented products of Withania somnifera. However, the process of fermentation for drug preparation is also described in ancient literatures of Ayurveda and also to some extent in Unani classical literatures for the preparation of Sirka, Nabeez, Dar Bahra, Aabkaama, etc. The use of fermentation for drug preparation is unpopular may be due to fear of contamination, time-consuming preparations etc. It is high time to upgrade the scientific research in India to achieve more efficacious drugs of herbal origin. The examples of the progress made by other system of medicine in the field of biotechnology, proteomics and genomics can be utilized in Indian system of medicines. By adopting the fermentation process, the therapeutic efficacy and bioavailability of medicinal plants may also be increased. Similarly, the toxicity of the treated drug may be decreased.

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

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