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Biological Evidence of Piperine: A review

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ABSTRACT

Piperine is the main compound present in black pepper, and is the carrier of its specific pungent taste, which is responsible for centuries of human dietary utilization and worldwide popularity as a food ingredient. Piperine has diverse biological activities, such as anti-inflammatory, anticancer, antiviral, anti-larvicidal, pesticide, anti-Alzheimer's, antidepressant, and most importantly piperine is known as the bioavailability enhancer. The current review article aims to explore various biological activities of piperine.

KEY WORDS: Piperine, chemical compounds, plants, bioactivities

INTRODUCTION

Among all spices, black pepper is well known as a distinctive spice worldwide. It is also known as the 'King of spices.' It has a distinctive pungent flavor due to the presence of an alkaloid piperine, along with volatile oils, and essential oils. The content of piperine varies from plant to plant belonging to the Piperaceae family and varies from 2% to 7.4% in vines of black and white pepper (piper nigrum). The amount of piperine content can be influenced by modifications in conditions of cultivation such as climate or drying conditions and the place of origin [1]. Piperine, the most abundant pungent principle present in black pepper. Piperine is a compound belonging to the alkaloids; it is responsible for the pungent taste of various pepper species, and has, in addition to being found in the members of the Piperaceae family, been detected in several other plant species (Rhododendron faurie, Vicoa indica, Anethum sowa, and others) [2]. The amount of piperine is highest in Piper nigrum L. and varies from2% to as high as 9% [3], depending on environmental factors such as climate and/or place of origin, as well as growing conditions. Investigations on piperine bioactivities have reported the very high spectrum of biological effects, including antihypertensive, antiaggregant, antioxidant, antitumor, antispasmodic, antiasthmatic, antidepressant, anxiolytic, and many others [4]. Along with an array of biological activities, piperine is known for its ability to increase the bioavailability of drugs, and thus enhance their therapeutic potential [5, 6]. Along with beneficial effects, piperine has, as the main ingredient of the most known spice, pepper, been traditionally used as a food for centuries, and does not present any threat upon human consumption. Additional studies have revealed the safety of its consumption by reporting a lack of piperine genotoxicity in Ames tests and in micronucleus tests [7]. This review showed the biological activities of piperine compound.

BIOLOGICAL ACTIVITIES

Anti-Cancer activity of Piperine

In vitro studies on various cancer cells showed that piperine possesses cytotoxic action (selective toward tumor cells) against several types of cancer, such as breast, lung, prostate, cervical, and other cancers.

Breast Cancer

Piperine inhibits AP-1 and NF-B activation, blocks extracellular signal-regulated kinase (ERK1/2), p38 mitogen-activated protein kinase (p38 MAPK), and Akt signaling pathways, and suppresses epidermal growthy factor (EGF)-induced MMP-9 expression [8]. Without affecting normal mammary epithelial cell growth, piperine inhibits the in vitro growth of triple-negative breast cancer cells (TNBC), and hormone-dependent breast cancer cells. Also, it increases the expression of p21(Waf1/Cip1) and inhibits survival-promoting Aktactivation [9], inhibits mammosphere formation, breast stem cell marker aldehyde dehydrogenase (ALDH), and Wnt signaling pathway without causing toxicity to differentiated cells [10].

Lung Cancer

Administration of piperine reduces DNA damage and DNA-protein cross-links in the lung cancer-bearing animals. In this study, mitochondrial enzymes (isocitrate dehydrogenase (ICDH), ketoglutarate dehydrogenase (KDH), succinate dehydrogenase (SDH), malate dehydrogenase (MDH)), glutathione-metabolizing enzymes GPx, GR and glucose-6-phospho dehydrogenase(G6PDH) were significantly reduced, while NADPH-cytochrome reductase (NADPH-C reductase), cytochrome P450 (cyt-p450) and cytochrome b5(cyt-b5) showed increased levels in mice administered with piperine [11]. Also, in these animals, ATPase enzymes in erythrocytemembrane and tissues were shown to be increased, while sodium/potassium/magnesium ATPase enzyme activities decreased, showing the chemopreventive effect of piperine [12].

Prostate Cancer

When investigating the effect of piperine to voltage-gated K+ channels (KV), which play an important role in regulating cancer cell proliferation and are considered as potential targets for the treatment of cancer, it was found that it blocks voltage-gated K+ current. It was effective in doses of IC50 = 39.91 µM in LNCaP and 49.45 µM in PC-3 human prostate cancer cells. This recorded blockade led to G0/G1 cell cycle arrest and consequently inhibited cell proliferation and induced apoptosis [13]

Cervical and Ovarian Cancer

Piperine and mitomycin-C (MMC) co-treatment resulted in inactivating STAT3/NFB, leading to suppression of the Bcl-2 signaling pathway in human cervical cancer. Also, this compound, together with its analogs demonstrated significant potential against Hela cervix cell line [14]. A recent study showed that piperine (8, 16, and 20 µM) inhibited cell viability and caused apoptosis in human ovarian A2780 cells via JNK/p38 MAPK-mediated intrinsic apoptotic pathway [15]. Further analysis on the mechanism of its action demonstrated increased levels of cyt-c from mitochondria and consequently increased caspase (caspase-3 and -9) activities and also decreased phosphorylation of JNK and p38 MAPK following piperine treatment.

Anti-Inflammatory activity

Piperine decreases liver marker enzymes activity (aspartate transaminase (AST), alanine,transaminase (ALT), and alkaline phosphatase (ALP)) in acetaminophen-challengedmice, indicating its hepatoprotective and antioxidant eff
ects [16]. Piperine decreases blood urea nitrogen (BUN), creatinine, and malondialdehyde (MDA), and increases superoxide dismutase (SOD), glutathione peroxidase (GPx) in the kidney of lead acetate-treated nephrotoxic rats [17].

Effects on CNS and Nerve Conductivity

The research proved that piperine is responsible for the analeptic activity which may expressed through due to its effect on nerve impulse transmission in the brain stem. Recently, pharmacological action of piperine and capsaicin has been proved to be shown due to its interaction with various transmitters, i.e., neuropeptides: substance P, neurokinins and calcitonin gene related peptide. These neurotransmittors are the agents of nerve transmission or communication present in various parts of the body [18-22].

Antioxidant Property

Piperine, naturally occurring spice component have good potential as antioxidant and hence utilized in nutritional and therapeutical preparations [23, 24]. Piperine is used as co-adjuvant for both treating as well as preventing the aging process and its related conditions like atherosclerosis, hypertension, diabetes, tumors, obesity, and overweight, hypertriglyceridemia, hypercholesteromia, skin aging, alopecia, panniculopathia (cellulite), osteroporosis, cerebral aging (Alzheimer, Parkinson, senile dementia etc.) and loss of memory, stress, depression, menopausal syndromes and benign prostate hypertrophy [25]. Another study concludes that

against diabetes induced oxidative stress can be protected with piperine treatment for 14 days using diabetes mellitus as a model of oxidative damage [26].

Analgesic Activity

Piperine was also isolate from the bark of Careya arborea, found to possess significant central and peripheral analgesic activity at oral doses of 10, 20 and 30 mg/kg body weight against acetic acid induced writhing in mice. However, piperine has prolongation of tail flicking time at doses of 20 and 30mg/Kg body weight by radiant heat method in mice [27]. Tasleem et al. evaluate and compare the analgesic and anti-inflammatory activity of pure compound, piperine along with hexane and ethanol extracts of Piper nigrum L. fruit in mice and rats and concludes that it possesses potent analgesic and anti-inflammatory activity at different doses by different methods [28]. Piperine intraperitoneally shows at 20 and 30 mg/kg by hot plate reaction test and acetic acid test in mice using indomethacin as a standard drug for reference [29].

Antidepressant effect

Piperine and its derivative, antiepilepsirine possesses antidepressant activity which was investigated in the depressive models like forced swimming test and tail suspension test. During this study determination of brain monoamine levels and the activities of monoamine oxidase A and B were carried out. The results show that in an assay of monoamines, chronic antiepilepsirine administration significantly elevates the dopamine level in striatum, hypothalamus and hippocampus, and also increases the serotonin level in the hypothalamus and hippocampus. In contrast, chronic treatment only with piperine enhances the level of serotonin in the hypothalamus and hippocampus but did not show any significant influence on the dopamine level. Moreover, both antiepileppsirine and piperine did not show any effect in the nonadrenaline level particularly in brain areas. The MAO activity assay also indicates that piperine and antiepilepsirine shows a minor MAO inhibitory activity. Liet in his study says that antidepressant potential of piperine was to be mediated via the regulation of serotonergic system, whereas antilepsirine antidepressant action might be mediated via dual regulation of both serotonergic and dopaminergic systems [30]. In another study, piperine has antidepressant like activity and cognitive effect during entire duration of treatment in Wister male rats at various doses ranging from 5, 10 and 20 mg/kg/day.

Antiplatelet Effect of Piperine

Fruits of the Piper longum contain piperine, piperonaline, piperoctadecalidine, piperlongumine which shows inhibitory potential on washed rabbit platelet aggregation [31]. All these acid amides show dose-dependent inhibitory activity on washed rabbit platelet aggregation and the acid amide Piperlongumine shows stronger inhibitory effect than other acid amides to rabbit platelet aggregation induced by collagen.

Effect on the Lipid Peroxidation

Piperine reduces the liver lipid peroxidation, acid phosphatase and oedema induced by carrageenin in rats. Thus, the study suggests that the liver enzymes are inhibited but they are nonspecific in nature [32]. Lipid peroxidation content, measured as thiobarbituric reactive substances (TBARS), was increased with piperine treatment although conjugate diene levels were not altered in a study carried out to determine the toxicity of piperine via free-radical generation by determining the degree of lipid peroxidation and cellular thiol status in the rat intestine. The study suggests that increased TBARS levels may not be a relevant index of cytotoxicity, since thiol redox was not altered, but increased synthesis transport of intracellular GSH pool may play an important role in cell hemostasis [33]. Oxidative stress occurs in association with painful exacerbations of chronic pancreatitis and antioxidant supplementation appears to benefit this condition. Thus, in another study, oral therapy of curcumin with piperine reverses the lipid peroxidation in patients with tropical pancreatitis. It was also observed that there was a significant reduction in the erythrocyte MDA levels and significant increase in GSH levels. There was no corresponding improvement in pain [34].

CONCLUSION

This review showed the importance of Piperine as a medicinal compound. Also it showed the therapeutic potential of piperine and the need to incorporate this compound into general health-enhancing medical formulations (especially those containing other well established antioxidants), as well as into those that could be used as adjunctive therapy in order to enhance the bioavailability of various (chemo) therapeutic drugs.

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