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Review Article

Piperine – An Immunomodulator and Inflammation Mitigator

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Abstract

Black pepper, one of the most widespread spices, gained the entitlement "King of spices" founded on its peculiar pungent test and therapeutic properties, both owed to its active alkaloid - piperine. Mounting evidence indicates that piperine possesses immunomodulatory and therapeutic activities. The aim of this mini review was to summarize the role of piperine in abolishing inflammation, its part in the immune activity of peripheral blood mononuclear- and a number of other cells, its capacity to elicit production of inflammatory cytokines and its function as a synergist endorsing the beneficial therapeutic effect of conventional anti-inflammatory drugs.

Keywords: piperine; black pepper; inflammation; macrophages; cytokines

Introduction

Nutrition has permanently been the main concern of humankind. Reasonable enough parallel with food our ancestors fostered senses of taste and made efforts to enhance flavor using spices that within time rapidly increased in quantity and quality. Moreover, hundreds of centuries ago our predecessors became aware that a great number of spices and herbs possess therapeutic properties. This knowledge prompt them to use plants for treatment of diseases and wounds, thus paving the way traditional herbal medicine became established and further developed [1]. Among the numerous spices in use today, one of the most broadly applied is the black pepper (*Piper nigrum*) which originated in India, but quickly spread worldwide and became the highly valuable *"King of Spices"* [2, 3]. Actually, the source of its distinct pungent flavor is attributable to one of its most active alkaloids - piperine. A significant number of studies have shown that piperine, in spite of its culinary qualities, possesses valuable physiological and medical assets, such as anti-inflammatory, antioxidant, antiseptic, anticancer and even antiepileptic properties that render it useful in a few acute and chronic health conditions detailed in comprehensive studies and reviews [4-10]. In addition, it has been found that piperine has pronounced immunomodulatory and biological properties [11]. The current concise review was designed to summarize the effect of piperine on the immune system, the capacity of human peripheral blood mononuclear cells to produce inflammatory cytokines, as well as the ability of this alkaloid improve the beneficial effect of certain drugs and spices.

Piperine, macrophages and cytokines.

It has been documented that piperine, either alone or in combination with other remedies, is effective in treatment of chronic diseases such as inflammatory conditions, diabetes and reduction of insulin-resistance, liver diseases and others [12]. Based on observations from traditional medicine that piperine exerts beneficial effects as an anti-inflammatory medication, researchers carried out studies to clarify the mode of its immunomodulatory activity [13]. Since macrophages are the main immune executors involved in inflammation the question arises as for the functional relationship between macrophages and piperine. Considering the fact that macrophage polarization that precedes inflammation is dependent in part on the intercellular adhesion molecules-1 (ICAM-1) Gholijani et al. [14] have shown that piperine restrains the inflammatory process by inhibition of ICAM-1 expression which is up-regulated during inflammation. Additionally, repressed expression of macrophages' ICAM-1 molecules improves their function in removing apoptotic and necrotic cells that accumulate following inflammation injury [15]. Furthermore, the anti-inflammatory activity of piperine is due to its ability to block TNFα induced expression not only of ICAM-1, but also of other cell adhesion molecules such as VCAM-1 (vascular cell adhesion molecule-1) and E-selectin [16]. Studies with mice revealed that piperine controls LPS stimulated peritoneal macrophages by strongly incitement of their mTORC1 activity operating as a regulator of protein synthesis and by increased IL-6 and TNFα production [17]. Consequently, the macrophages upsurge their phagocytic capacity, avoid apoptosis and amplify their antibacterial ability. The proficiency of piperine to modify inflammatory cytokine production by macrophages is important. It was found that IL-1β, a cytokine tightly involved in the inflammatory pathway, produces a complex in the presence of piperine, thus preventing the activity of the cytokine in the progress of inflammation [18]. In mice with traumatic brain injury piperine was shown to decrease seizures by reducing the production of the pro-inflammatory cytokines TNFα and IL-1β [19]. According to Liang at al. [5] administration of piperine to LPS stimulated macrophages and to Escherichia coli infected mice caused a remarkable decrease in IL-1β production with suppression of

inflammation and pyroptosis. The compelling anti-inflammatory potential of piperine and its ability to suppress cytokine storms, such as those observed in severe cases of COVID-19 infections, prompted researchers to suggest it as an adjuvant in the therapeutic efforts against this outbreak [20, 21]. Research on the anti-inflammatory properties of long pepper (*Piper longum*) and cubed pepper (*Piper cubeba*) extracts containing piperine has been carried out on LPS induced THP1 monocyte derived macrophages. The results showed that these extracts are able to reduce dose-dependently the secretion of the main pro-inflammatory cytokines TNFα and IL-1β [22]. LPS treated mouse macrophages (RAW 264.7 cells) stimulated by piperine showed subdued production of prostaglandin E2 and nitric oxide, as well as that of TNFα, inducible NO synthase (iNOS) and COX-2 [23]. Chuchawankul et al. [24] detected a noticeably inhibited cell proliferation of human peripheral blood mononuclear cells (PBMC) exposed for 72 hours to piperine. According to the authors this phenomenon is due to suppressed T cell proliferation since these are the major proliferating cells when PBMC are stimulated by PHA. In addition, the production of IL-2 and IFNγ by PHA activated PBMC was dose-dependently inhibited. Higher piperine concentration remarkably reduced these cytokines secretion, findings indicating a strong relationship between cell proliferation IL-2 and TNFα production. The anti-inflammatory properties of piperine have been observed in obesity induced inflammation [25]. The authors treated Raw 264.7 macrophages with rat adipose tissue-conditioned medium and exposed the cells to piperine, as well as to various spice-derived components and observed a markedly dose-dependently inhibited macrophage migration. However, in difference from the other spice derived components used in the study that of piperine did not affect the production of TNF-α.

Piperine and cytokine production by cells other than macrophages.

It appears that piperine exerts anti-inflammatory properties in cells other than monocytes and macrophages. CTLL-2 T lymphocytes treated with piperine have shown an inhibited IL-2 signaling [26]. In addition, piperine was able to inhibit T cell proliferation and suppressed T cell transition through the mitotic S and G2/M phase and to restrain the generation of IFNγ, IL-2, IL-4 and IL-17A [27]. In an asthma mouse model piperine inhibited the production of Th2 cytokines i.e. IL-4 and IL-5 in the bronchoalveolar lavage fluid and the immunoglobulin E production in the serum [28]. Based on these findings piperine was suggested by the authors to be considered as an additional treatment modality of autoimmune diseases. It has been revealed that piperine possesses a noticeable affinity towards CD4 and CD8 T cell receptors, increases cell viability and restores cytokine production by deltamethrin injured cells, characteristics that may clarify its immunomodulatory role [29]. Piperine applied on IL-1β stimulated synoviocytes obtained from patients with rheumatoid arthritis remarkably inhibited the production of the pro-inflammatory cytokines IL-6 and PGE2. Given orally to rats with collagen induced arthritis piperine significantly reduced the production of the pro-inflammatory cytokines IL-1β, TNFα and PGE2 and increased the level of the anti-inflammatory cytokine IL-10 [30]. Similar inhibition of the pro-inflammatory cytokines was observed when piperine was administered intraperitoneally to mice with LPS-induced mastitis [31]. The secretion of the pro-inflammatory cytokines TNFα, IL-6, IL-1β and PGE2 by LPS stimulated BV2 cells, that are microglial macrophages in the central nervous system, was reported to be subdued by piperine [32]. In an animal model with *Staphylococcus aureus* endometritis piperine inhibited the inflammatory process and reduced the expression of TNFα, IL-1β and IL-6, while that of the anti-inflammatory cytokine IL-10 was increased. The authors showed that the effect of piperine was due to inactivation of NF-kB and MAPKs pathways, both controllers of inflammatory cytokine production [33]. Piperine treated LPS stimulated mouse dendritic cells showed a reduced expression of the pro-inflammatory cytokines IL-6 and TNFα as well as a reduced migration towards lymph nodes [34]. Treating bone marrow derived LPS stimulated dendritic cells with piperine Bae at al. [35] documented a suppressed production of TNFα and IL-12, while the expression of IL-6, also a pro-inflammatory cytokine, was not affected. According to the authors these findings proceeded through inhibition of stress-related c-jun N-terminal kinases (JNK). Notably, not only piperine itself but also black pepper (*Piper nigrum*) aqueous extracts exert an immunomodulatory effect expressed by a dose dependent proliferation and increased production of T helper-1 cytokines by splenocytes, whereas the generation of T helper-2 cytokines was reduced [36]. Alagawany et al. [37] supplemented the diet of birds (quails) with red and black pepper oil mixture and reported that their antioxidant and immunity parameters became statistically improved compared to controls. Mice with thymic atrophy and splenomegaly induced by cadmium, known by its immunotoxicity, showed marked recovery in body weight, cell viability and restored IL-2 and IFNγ secretion after administration of piperine [38,39].

Piperine as a synergist.

The beneficial effect of piperine on inflammatory reactions can be amplified when administered jointly with conventional therapeutic remedies. The favorable results obtained by administration of thymoquinone on the hepatotoxic and neurotoxic effect observed in mice given microcystin were markedly intensified when it was delivered together with piperine and were expressed by both improvement of the liver and brain biochemistry tests, as well as with a marked decrease in the production of the pro-inflammatory cytokines IL-1β, IL-6 and TNFα [40]. The therapeutic activity of piperine has been shown to be more pronounced when administered with natural alkaloids extracted from plants and fruits. In a murine model of systemic lupus erythematosus piperine combined with resveratrol suppressed the level of the pro-inflammatory cytokines TNFα, IL-6 and IFNα indicating a potential therapeutic capacity of these alkaloids [41]. In a mouse model of *Mycobacterium tuberculosis*, treatment of splenocytes concomitantly with piperine and rifampicin induced an enhanced activation of Th-1 lymphocyte response with an increased production of IFNγ and IL-2 compared with that obtained with each one of the above components given alone [42]. Oral medication of rabbits with ampicillin and norfloxacin supplemented with piperine improved the bioavailability of the antibiotics [43]. Administration of piperine with a variety of spices has been shown to produce an additive positive biological and pharmacological effect. Piperine given with curcumin was able to abolish the oxidative stress and caspase 3 of deltamethrin known to exert a potent immunotoxic effect in both humoral and cell mediated immunity. However, in vitro studies indicate that phenotypic and cytokine changes are better expressed with piperine compared to curcumin [44]. In patients with type 2 diabetes given curcumin and piperine the serum levels of adiponectin, leptin, and TNF-α were lower than those given placebo [45]. Treatment of iron deficiency with iron preparations supplemented with piperine improved iron absorption and its bioavailability [46]. It has been reported that piperine, at its liposomal formation, promotes the antibacterial activity of gentamicin and exerts better effect against MERSA infections [7, 47]. Piperine may increase of bioavailability of phenytoine, propranolol and theophylline in healthy volunteers detected by plasma concentration curve (AUC), an activity that should be considered in cases with seizures, heart conditions and lung diseases. In patients with pulmonary tuberculosis the plasma concentrations of rifamipicin was been found to be elevated [48]. In addition, investigations showed that piperine may act as a synergist to tetracycline, an observation that could be useful for the treatment of bacterial infections [49]. Combined administration of piperine with natural polyphenolic compounds, such as curcumin, luteolin, and resveratrol are capable to restrain the immense release of pro-inflammatory cytokines such as TNFα, INFγ, IL-1β, IL-2, IL-4, IL-6, IL-7, IL-9, IL-10, IL-12, IL-13, IL-17, G-CSF, GM-CSF, MCSF, HGF occurring during cytokine storms in

immunocompromised patients including those with COVID-19. [50]. It has been reported that piperine exerts a significant radioprotection in irradiated human lymphocytes expressed by a marked diminution of micronuclei number compared with irradiated non piperine-treated cells. This effect was more impressive when the lymphocytes were pretreated with both piperine and curcumin [51]. Rats given piperine before irradiation showed lesser elevation in serum TNF-α, IL-1β and IL-6 [52].

Side effects

The widespread consumption of black pepper poses the question if the spice may induce adverse effects. The immunotoxic events of piperine have been investigated in mice given the alkaloid at doses of 1.12, 2.25 or 4.5 mg/kg body weight for five days. No toxic effects were noted at these doses, but higher ones, i.e. 2.25 and 4.5 mg/kg, hematologically administered, resulted in a reduction in total leucocyte counts with an increase in the neutrophils' percentage. These doses suppressed the mitogenic response of B-lymphocyte to lipopolysaccharide. The authors' conclusion is that the dose of 1.12 mg of piperine per kg body weight may be considered as immunologically safe since it is deprived of immunotoxicity [53]. In another study feeding rats with piperine at doses of 0, 5, 15, or 50 mg/kg per body eight for 90-days no adverse effects we observed [54].

Conclusion

Summarizing the presented data it may be stated that piperine exerts an immunomodulatory activity not only by prompting PBMC capacity for anti-inflammatory cytokine production, but also by affecting the immune activity of lymphocytes and a number of other cells. Piperine, as an immunomodulator, may express beneficial synergistic effects with other drugs and spices, virtues that permit to affix a number of medical benefits to a renowned appetizing spice.

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