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Piperine: A review on different formulations and pharmacological activities

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Abstract: Heterocyclic compounds are taking up an important position in heterocyclic chemistry due to their constructive properties as therapeutic agents, drugs, dyestuffs etc. Heterocyclic compounds have detained core point in the progress of molecules to enhance quality of human life. For example, more than seventy percent of drugs used nowadays are heterocyclic compounds. They are extensively distributed in nature and are key intermediates in many biological processes. A number of natural products are heterocyclic in nature and are constitutive molecules in human body. Among various natural products piperine has revealed several health effects and favourable medicinal properties such as antimicrobial and antifungal, antitumour activities, antiinflammatory, anti-arthritis, anti-ulcer, and antidepressant, antiulcer, analgesic, antioxidant, antithyroid, immunomodulatory and among others. However, low solubility of piperine in water create some difficulties in delivery of drug and medicinal applications. To improve the bioavailability of piperine, various development in the preparation of new formulations containing piperine have been reported in the literature. This review presents development of new formulations and various pharmaceutical applications of piperine.

Keywords: Piperine, chemical constituents, bioenhancer, formulations, and pharmacological activity.

1. Introduction

Natural products have been the source of survival for mankind [1]. A number of natural products are heterocyclic in nature and are constitutive molecules in human body. These includes constituents of biopolymers such as vitamins, amino acids, purines, pyrimidines. And part of oxygen transport proteases e.g. hemoglobin and myoglobin. Heterocycles have also served as various drugs and presenting greater than 70% of drugs are from different classes of heterocycles. A number of natural products containing heterocyclic moieties have served as either medicine or lead molecule for the development of drugs [2]. One such molecule is piperine,an alkaloid, along with several other volatile chemical constituents and essential

oils, is responsible for pungency in black pepper. Black pepper, white pepper and long pepper, all of which belong to the Piperaceae family, contain various amounts of piperine. In black and white pepper (piper nigrum) vines, the piperine content shows a discrepancy of 2 to 7.4 percent. A higher piperine content of up to 9 percent in black pepper and 4-5 percent in long pepper (Piper longum) was suggested in some studies, however [3]. The total amount of piperine content varied with changes in the environment of cultivation, such as climate conditions, place of origin or drying process [4].

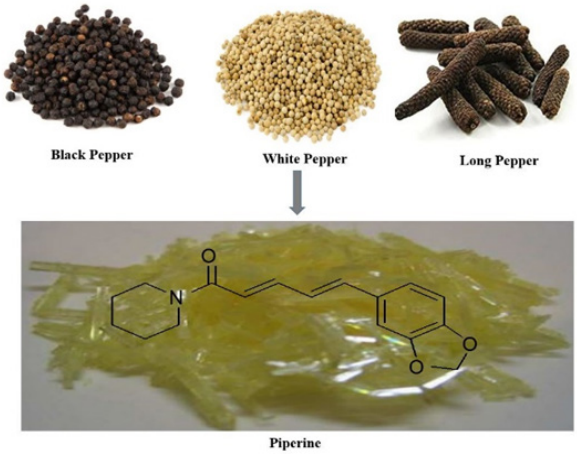

Fig.1. Different sources of piperine.

Because of its diversity in medicinal properties, Black pepper a natural spice is commonly integrated in various foods has been well mentioned in various traditional medicines [5]. The Latin name Piper nigrum (piper meant plant and nigrum meaning black) is plagiaristic. In ancient greece, the history of black pepper as a spice is really ancient, since the era of the pyramids (2600-2100 BCE). The 'King of Spices' or 'Black Gold' is also known. With 47% to 53% carbohydrate, 11% to 14% calcium, and 10% to13.5% starch, black pepper has a high nutritious value [6]. It is also composed of magnesium, manganese, potassium and vitamins K and C in significant amounts. The odour and flavour of pepper plants are attributed to terpenes and their derivatives contained in pepper essential oil [6-7]. The essential oils in black pepper are derived from seeds and from leaves. Furthermore, to be present in this valuable spice, more than 250 volatiles have been recommended. In addition to piperine, some other black pepper components are pipericide, eugenol, and (-)-cubebin, as seen in Fig.1. Germacrene D, limonene, β-pinene, β-phellandrene, β-caryophyllene, β-pinene, and cis-β-ocimene are many other detected compounds.

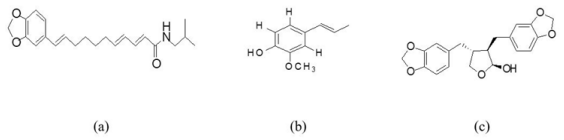

Fig. 2.Some others active chemical constituents of black piper (a) Pipericide (b) Eugenol (c) (-) – Cubebin.

In 1819, Piperine was firstly isolated by Hans Christian Orsted. The chemical structure was elucidated with chemical formula of $C_{17}H_{19}NO_3$, and IUPAC name as 1-(5-[1, 3-benzodioxol-5-yl]-1-oxo-2, 4-pentadienly) piperidine. Piperine, which can be converted to piperic acid ($C_{12}H_{10}O_4$) and piperidine ($C_5H_{11}N$) on acidic / basic hydrolysis [8], is weakly basic in nature. Piperine (trans-trans isomer), isochavicin (trans-cis isomer), chavicine (cis-cis isomer) and isopiperine (cis-trans isomer) are four geometrical isomeric piperine structures, as seen in Fig. 2. The three geometric piperine isomers, however, have virtually no pharmacological function [9]. Isomerisation increases with increasing light intensity and exposure to time. Light-induced isomerization, which can be transmuted into isopiperine2, chavicine3 and isochavicine4, was also observed in piperine. On storage, shifts in chavicine to piperine can

be seen that contribute to the loss of pungency slowly and immediately [10]. The presence of other alkaloids in the pepper extract, including piperanine, piperettine, piperylin A, piperolein B, and pipericine, most of which contain some degree of pungency, has been confirmed by further investigations with piperine.

However, the overall contribution of these alkaloids to pungency of pepper was found to be small. In spite of argument over the nature of the compounds responsible for pungency of pepper, piperine is considered the principal pungent one of pepper as it constitutes around 98% of the total alkaloids in pepper [11] and; thus, the piperine content is taken as a measure of total pungency of pepper [12].

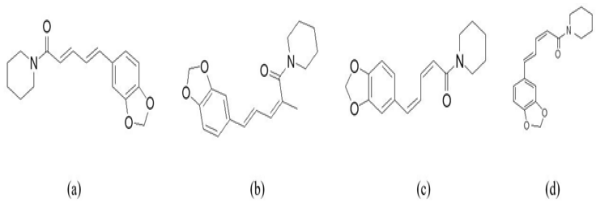

Fig.3. Structure of piperine and its isomers (a) Piperine (b) Isoprene (c) Chavicine (d) Isochavicine.

ning methods has led to several new drug entities being discovered. But there is a disadvantage in using several new chemical entities, as about 40 to 70 percent of them have insufficient aqueous medium solubility and rate of dissolution [13-14]. Therefore, in order to accomplish the therapeutic benefits of these active molecules, the selection of suitable methods to bypass the solubility problem is absolutely critical. The Piperine has poor solubility in water as well as high first-pass metabolism [15]. Low solubility results in a restricted rate of dissolution. Subsequently, it results in low bioavailability of orally administered medicines. Different studies have shown that piperine has different pharmacological activities, but piperine's poor solubility limits its pharmaceutical application because a higher dose of drugs is expected to be used to obtain the expected pharmacological response. Low solubility results in a limited rate of dissolution. Eventually, it results in poor bioavailability of orally administered medications. Different studies have also shown piperine has different pharmacological activities, but piperine's poor solubility limits its pharmacological application since a higher dose of drugs is expected to have been used to obtain the expected pharmacological response. It is also essential to sustain the solubility of piperine in order to prevent dose intensification and toxic effect [16-17].

In the present work, we have reviewed different formulations of piperine that are reported to improve its solubility. The next section pertains to various methods reported to achieve solubility of piperine.

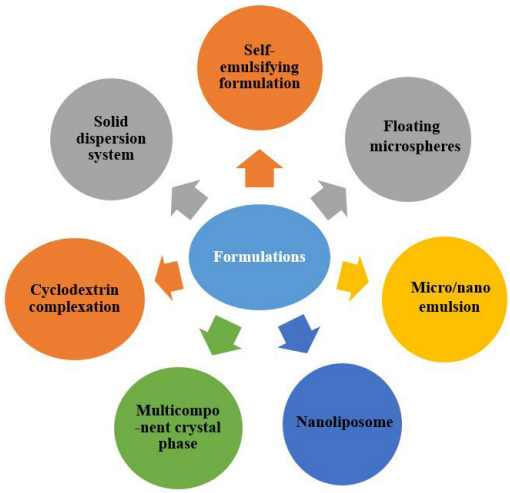

Fig.4.Various formulations of piperine.

1. Formulations of piperine

Various formulation such as development of a solid dispersion system with several polymers and water-soluble carriers [18-19], self-emulsifying drug delivery system, cyclodextrin complexation [20-21], formation

of a multicomponent crystal phase [22], floating microspheres, solubilization of drugs in solvents [23], and the reduction of the particle size to nanoscale [22, 24- 25], micro/ nanoemulsion [26], lipid nanoparticles [27], salt formation [28], and nanoliposome [29] of piperine have been used to investigate the enhancement of solubility/dissolution rate and in vivo bioavailability.

1.1. Solid dispersion system (SDs)

Sorbitol (Sor), polyethylene glycol (PEG) and polyvinyl pyrrolidone K30 (PVP) were used by Thenmozhi et al. to prepare solid piperine dispersions using a solvent method to prepare SDs by dissolving the drug and carrier in an appropriate solvent, followed by solvent evaporation to obtain the amorphous SD as a powder. The findings of their analysis revealed that, relative to physical mixtures and pure piperine, Sor, PEG and PVP showed superior efficiency for the dissolution of piperine with a drug release of approximately 70 percent, 76 percent and 89 percent respectively after 2 h. Data indicated that piperine solid dispersions prepared with enhanced in-vitro release had a potential benefit as an oral supplement in the distribution of poorly water-soluble piperine [18].

1.2. Self-emulsifying formulations

To describe the optimised formulation, solubility studies, particle size evaluation and drug release were used to study the formulation of piperine. Single pass intestinal perfusion (SPIP) in situ was also carried out to consider the mechanism of absorption. After that, the piperine SEDDS formulation's comparative bioavailability was connected with the self-prepared capsules in rats [30]. To describe the optimised formulation, solubility tests, particle size measurement and drug release were used to evaluate the formulation of piperine. Single pass intestinal perfusion (SPIP) in situ was also carried out to consider the mechanism of absorption. Finally, the piperine SEDDS formulations comparative bioavailability was correlated with the self-prepared capsules in rats [30].

1.3. Cyclodextrin complexation

The synthesis of the inclusion complex of piperine with EN-β-CD was effectively carried out using the co-precipitation process in 2020 [31]. Piperine and EN-β-CD were completely dissolved in a combined solution of deionized water / anhydrous ethanol (10% (v / v)) using this process. The resulting mixture was mixed for 4 h at 40 ° C. The uncomplexed piperine was filtered after vaporising the ethanol from the mixture. The filtrate obtained was vacuum dried for 12 h at 40 °C. Piperine's encapsulation efficiency (EE) was influenced by reaction time and reaction temperature. Increased reaction time and temperature were first quickly and then slowly increased by EE. Piperine complexation with EN-β-CD reaches equilibrium and maximal EE at a reaction time and temperature at about 4hr and 65 ° C respectively, then after EE declines [31].

1.4. Multicomponent crystal phase

Studies in 2017 and 2018 based on the development of piperine multicomponent crystals in the presence of a resveratrol cocrystal and a halide salt, respectively [32-33]. Hydrogen bonding between the oxygen atom of the piperine and water ketone and the hydroxyl group of resveratrol develops as piperine forms a cocrystal with resveratrol. An inorganic salt with usually used reagents such as HCl or HBr should not form piperine [33]. Therefore, cocrystal formation with organic acids is needed for the preparation of the multicomponent crystal of piperine. Therefore, for a molecule that has a hydrogen bond donor

group, piperine is expected to form a cocrystal. Zaini et al. recently prepared piperine-succinic acid cocrystals by using slurry procedure [22].

1.5. Floating microspheres

In 2012, ethyl cellulose, hydroxypropyl methyl cellulose and carbopol were used for the preparation of floating piperine microspheres by Boddupalli et al. [34]. Khatri et al. prepared floating microsphere-containing piperine in 2016 by dissolving acyclovir, ethyl cellulose in dichloromethane. It was observed that particle size increased with an increase in polymer concentration, and microspheres ranged from 400 to 525 μm in size. This may be attributed to the fact that the increasing polymer concentration increases the viscosity of the solution, and the matrix density of the microspheres has also improved. Further, the particle size was improved with the addition of piperine. This may be attributed to improved interfacial stress and decreased performance of shearing [35].

2.6.Micro/nanoemulsion

First of all, in the oil phase, piperine, egg lecithin and cholesterol were dissolved, heated in a water bath to 70 °C, and stirred until the piperine was dissolved. The aqueous phase comprising of glycerol, sucrose and sodium oleate at the same temperature (70 °C) was applied to this oil phase. By homogenization and emulsion, a rough emulsion was formulated such that the LN drug delivery device was exposed to ultrasonication for 20 minutes.

2.7. Nanoliposome

Drug efflux is the key mechanism exhibited by various Gram-ve bacteria. With these pumps micro-organism regulate the internal environment by saluting out the toxic substances including anti-microbial drugs. Piperine has the potential to inhibit bacterial efflux pumps, especially when used in combination with antibacterial agents [36-37]. The antibacterial activity of antibacterial agents is also improved in conjunction with piperine. To test the antibacterial activity, piperine in combination with gentamicin was used. In order to determine an acceptable means of administering hydrophilic gentamicin along with hydrophobic piperine, it is convinced to find an appropriate way to administer mixed formulations.

Liposomal formulations containing gentamicin were prepared by solvent evaporation method. Liposomes consisted of Egg PC, Chol and piperine (in liposomal combination), and extruded through polycarbonate filter by extruder. The gentamicin solution was added to liposomal suspension. The liposomal mixture was kept in freezer. The frozen liposomal mixture dried in a freeze drier for 12h. The dried material was rehydrated by distilled water to form the liposomal suspension. Non-entrapped gentamicin was separated by centrifugation of liposomes and then liposomes were washed twice [38].

2. Applications of piperine in drug delivery

Piperine is widely used in ancient Chinese and Indian medicine to control the pain, rheumatism, arthritis, influenza, chills, and fever [39]. Piperine has various biomedical effects, along with pain control [40], hypotension, stimulation of vascular cells [41-42], and function toward cancer [43]. It is also noted that piperine can be used to strengthen blood circulation, saliva flow, and appetite enhancement [44]. Some studies has shown that piperine has functions that are chemopreventive and antioxidant. Piperine (including p-glycoproteins) also functions on many enzyme systems [45-46].In addition to all these, piperine has shown various biological

and pharmacological applications, such as anti-infective, antimicrobial and antifungal [47], anti-amoebic [48], insecticidal [49-51], antitumour Correa activities [52], antiinflammatory [53-54], anti-arthritis[55], anti-ulcer, and antidepressant [56], antimetastatic, antiulcer, antipyretic, analgesic[57-58], antioxidant [47, 59-60], hepatoprotective [61], antithyroid, immunomodulatory and antitumor [42].

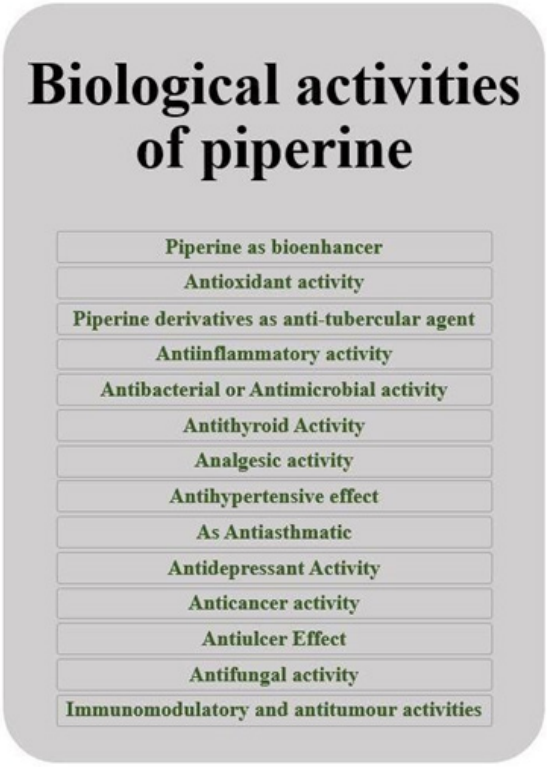

Fig.5.Various biological activities of piperine.

2.1. Piperine as Bioenhancer

When used in combination of drugs across distinct paths, bio-enhancers can improve the efficacy of drug molecules through enhancing the bioavailability of a drug through the membrane (increasing amount of drug in the blood stream accessible for drug action), increasing the effect of the drug through conformation interaction and acting as a drug receptor [62]. Several experiments have shown that piperine improves the absorption and bioavailability of various molecules of drugs [63-64]. A literature has explored that piperine absorption is very fast across the intestinal barrier. This work showed that, due to the nonpolar nature of piperine, piperine has a passive diffusion function, a high apparent permeability factor, and a limited clearance period [65]. Piperine can change the membrane dynamics by interacting with hydrophobic sections of the protein and lipids. In addition, the conformation of enzyme proteins has been modified by a decrease in the property of membrane lipids to act as steric constraints on enzyme proteins.

Combinations of the antibiotic rifampicin with piperine, reported by Balakrishnan et al., substantially increased the inhibitory effect on Mycobacterium smegmatis compared to rifampicin alone. The inhibition effect of the enzyme piperine is responsible for the liver digestion of these antibiotics, which may be the source of their improved bioavailability [66]. The bioavailability of β-lactam antibiotics such as cefotaxime sodium, amoxicillin [67], and ampicillin and other forms of antibiotics such as norfloxacin have been improved by piperine in other research [68]. It has also been found that by inhibiting the enzymes responsible for the liver synthesis of gatifloxacin in laying hens, piperine can enhance the pharmacokinetic effects of gatifloxacin (an antibacterial agent) [69]. Johnson et al. testified that by inhibiting its metabolism and decreasing the necessary dosage of resveratrol in a therapeutic setting, piperine greatly improved resveratrol's in vivo bioavailability [70]. Docetaxel (cytotoxic chemotherapeutic agent) has recently been used in metastatic castration-resistant prostate cancer (CRPC) as the most effective medicine. The antitumor activity of docetaxel in the human CRPC xenograft model was enhanced by co-administration of piperine with docetaxel [71]. Piperine also enhances the bioavailability of traditional and herbal medications such as curcumin and resveratrol [72]. Piperine also

boosted the bioavailability of curcumin and enhanced its preventive impact against cognitive disorder and subsequent oxidative destruction in mice induced by chronic unpredictable stress (CUS). Curcumin bioavailability improvement may be attributed to the protective impact of piperine on curcumin's intestinal and hepatic metabolism [73]. Another research stated that dual-drug-loaded nanoparticles containing curcumin-piperine (Cu-Pi) were able to resolve low oral bioavailability of curcumin and cancer cell targeting constraints in cancer treatment [74]. Curcumin also optimized the oral bioavailability and tissue distribution of curcumin with piperine-loaded cubosome nanoparticles [75]. There is a plethora of data supporting the fact that piperine has diverse pharmacological functions that modulate the activities of transporters and metabolic enzymes. In addition, it is proposed that it is possible to use piperine as an alternative medication [76].The conceptualization of bioenhancers or biopotentiators is called 'yogavahi' in Ayurveda. In order to improve the bioavailability of poorly absorbed medicines, Tiwari et al. compiled various ayurvedic formulas, the Unani medicine system and the Siddha Medicine System [39]. The mode of operation of different herbal bioenhancers may be identical or different. In both conventional and modern sciences, the bioenhancing effect of the pepper class is feasible due to two major mechanisms; one is due to a general mechanism in which lowered secretion of hydrochloric acid could be observed through quick absorption of the compound. It also increases the influence of gamma-glutamyl transpeptidase as well as the flow of blood to the GI tract [77]. Next, by decreasing the rate of elimination and hindering the enzymes involved in the biotransformation drugs. The Atal C. K. Analysis. Piperine was shown to be an inhibitor of ethylmorphine-N-demethylation, arylhydrocarbon hydroxylation (AHH) and 7-ethoxycoumarin-O-deethylation in a dose-dependent manner in rat postmitocondrial supernatant [78].

Athukuri B. L. et al. reported the effect of piperine on the pharmaco kinetics of domparidone-treated animals with a dose of 20 mg/kg via both an intraperitoneal as well as oral route. The results suggested that there is a minor increase in mean plasma concentration, elimination half-life, area under the curve of the domparidone when given in combination with piperine [79] Singh A.et al. reported the effect of piperine on the pharmacokinetic profile of rifampicin and isoniazid, alone or in combination with piperine. Results suggested that, the coadministration of rifampicin with piperine results in relative bioavailability of 141.7%, and for theisoniazid, the relative bioavailability was found to be 67.19% [80].In-vitro and in-vivo studies performed by Junsaeng et al. concluded that the intake of oxyresveratrol in combination of piperine improves the various pharmacokinetic properties of oxyresveratrol via both intravenous and oral administration. [81]Gabhe et al. reported that piperine shows significant changes in the pharmacokinetic profile of simvastatin (10 mg/kg), and secnidazole (10 mg/kg) when given alone and in combination with a fixed-dose of piperine (10 mg/kg). Piperine exhibits 2.53, and 1.08 fold increases in the bioavailability of these drugs, respectively [82-83]

3.2. Effect on digestion

The effect of various spices on the body's metabolism was examined by Shrinivasan et al. [42]. The development of saliva and gastric secretions is stimulated by piperine [42]. Similarly, peppercorn consumption enhances salivary amylase development and activation [84], which is likely to induce the liver to secrete bile and help digest food. In 2011, Hussain et al. observed that oral piperine administration could increase liver bile acid secretion [85]. Consumption of peppercorn

in food substances or oral administration of active genus piper compounds such as piperine, piperamides, piperamines and pipene has an effect on the enzyme activation of small intestinal mucosa pancreas , liver and terminal digestive enzymes [86-87].The inclusion of piperine as an additive in foodstuffs increases the production of digestive enzymes such as lipase development, amylase activity, activity of chymotrypsin and protease activity [88].The density functional theory (DFT) and the Hartree Fock (HF) methods were used to approximate the circulation of piperine in body tissues. These techniques were refined and calculations revealed that piperine dissolves quickly in the blood and enters the tissues of the human body. By reaction with the radical forms, due to low solubility, the unfavourable results are minimised and the damage to the cell structures is prevented [89].

3.3. Antioxidant activity

The significance of natural antioxidants, which are mainly present in plants due to their non-toxic and eco-friendly nature, has been dramatically increased [90]. The antioxidants obtained from plants are also used as food additives [90-91]. Exposure to radiation and environmental pollutants, tissue injury, infections, and autoimmune processes can lead to the production of free radicals [92]. In our body, when free radicals are produced, membranes attack and cause loss of different enzyme and receptor activities and cell inactivation by destroying the membrane proteins [90, 93]. The presence of free radicals in many diseases has also been found [94]. Some of the free radicals cause cancer, first targeting cell DNA by free radicals and then DNA inducing mutational modifications that eventually caused cancer [95-96].

Natural antioxidants are of concern to researchers to treat cellular degeneration related to several diseases [97-98]. Plants have evolved a complex antioxidant mechanism [90, 97] to prevent carcinogenesis and cell damage from reactive oxygen species (ROS) and reactive secondary metabolites (produced during metabolism) [42]. Enzymes such as Peroxidase (POD), Catalase (CAT), Superoxide dismutase (SOD) and Ascorbate (ASC), which scavenge both radicals and their corresponding non-radical oxygen species, are part of the antioxidant protection system.The effect of piperine on lipid peroxidation of tissue, enzymatic, and non-enzymatic antioxidants in rats fed a high-fat diet was studied in one report. Piperine lowers the amounts of reactive compounds such as acid and conjugate dienes and retains the levels of glutathione, glutathione peroxidase, catalase, superoxide dismutase, glutathione-S-transferase and the levels of glutathione-S-transferase production similar to that of control rats. Overall, the findings of their research suggest that piperine can minimize the high-fat oxidative stress caused by the high-fat [99]. DPPH (1, one diphenyl-2picrylhydrazyl) free radical assay assessed the antioxidant activity of the solvent extracts and observed that the ethanol extract exhibited a strong antioxidant activity owing to the highest volume of total phenolics present in it. The water extract revealed the lowest behavior in radical scavenging. Owing to the existence of phenolics that are missing during black pepper preparation, green pepper has high potency as an antioxidant. Therefore, as antioxidant agents, new spices and their extracts can be used [100].Chen et al. encapsulated both curcumin and piperine inside the CPZCCa^{2+} (curcumin-piperine-zein-carrageenan) nanoparticles. And, there was a 3.5- and 2.2-fold increase in the photostability of the curcumin and piperine in the CPZCCa^{2+}nanoparticles as compared to free curcumin and piperine, respectively [101].

3.4. Piperine derivatives as anti-tubercular agent

The influence of piperine on tuberculosis was investigated by Hegeto et al.; the 3D structure and binding affinity of M. Tuberculosis (Rv1258c) was studied using the technique of silicon molecular simulation. The minimum inhibitory concentration (MIC) for the anti-tuberculosis agents (rifampicin, ethambutol and streptomycin) was measured in this analysis, alone and in conjunction with piperine, by using Resazurin as a guideline accompanied by a microtiter assay. When combined with piperine (RIF + PIP and SM+ PIP), synergism in efflux pump inhibitor (EPI) activity was observed. The researchers proposed the antitubercular activity of piperine on the mycobacterial putative efflux protein overexpression [58]. The operation of some of the piperine analogues against mycobacterium tuberculosis (H37Rv) was reported by Philipova et al. The findings revealed that greater anti-tubercular action was demonstrated by the piperine analogues than ethambutol. One of the piperine amide derivatives selected demonstrated greater activity than isoniazid. The quantitative structure-activity relationship has shown that the main and concomitant prerequisite for the anti-tuberculosis effect is the substitution of the piperidine ring with the quaternary ammonium moiety [102].

3.5. Antiinflammatory activity

The anti-inflammatory role of piperine was carried out in several rat models in 1990 by Mujumdar et al. [54]. Singh and Duggal reported that P. nigrum-isolated piperine inhibits the attachment of endothelial monolayer to neutrophils, inducing tumour necrosis factor blockage- α -induced expression of intercellular adhesion molecules-1, vascular cell, and E-selectin [103]. Pro-inflammatory cytokines (GMCSF, IL-6, TNF- α and IL-1β) were reduced by piperine administration [104] and inhibited the expansion of genes that encode nitric oxidesynthase and cyclooxygenase-2 [104].Another blocking system stated by Vijayakumar et al. was that piperine inhibits the phosphorylation and degradation of IκBα by attenuating tumor necrosis factor-α induced IκB kinase activity [99]. The collagen matrix attack of melanoma cells was blocked dose-dependently by piperine in different concentrations (B16F-10) [105]. In 2009, Bang and Oh et al. reported that piperine was an anti-inflammatory, antiarthritic, anti-aging agent and Interleukin (IL) 1β activated synoviocytes were confirmed in the arthritic model. The study outcomes revealed that piperine acts in a dose-dependent manner and can act by inhibiting COX-2 and, more precisely, by inhibiting prostaglandin E-2 (PGE-2) development, relative to IL-6 by ELISA and RT-PCR analysis [55]. In 2010, Liu et al. recorded that at a concentration of about 25μg/mL, piperine inhibits the cyclooxygenase (COX) enzyme by 30 to 80 percent at a concentration of about 25μg/mL [106]. In 2014, the hexane and ethanol extracts of piper nigrum L were investigated by Tasleem et al. It exhibits extraordinary analgesic and anti-inflammatory activity [107]. In 2015, Dong et al. reported the effect of piperine on periodontitis by dramatically preventing dose-dependent alveolar bone degradation and tissue breakdown; the effect of piperine on interleukin-1β and metalloproteinase-8 (MMP-8) and 13 (MMP-13) inhibition is accredited. Therefore, it was inferred that piperine provides the periodontitis model with strong anti-inflammatory action [108]. In 2015, Hu et al. stated that piperine serves as an agonist that induces the Pregnane X Receptor (PXR), which further induces gene expression of the enzyme CYP-3A4 at levels of protein and mRNA. The findings show that by activating the PXR receptor, piperine can prevent and inhibit the activity of colonic inflammatory disease by CYP450 expression [109]. In 2017, by using a murine bronchial model, Kim and Lee et al. testified that piperine is a major component in inhibiting bronchial asthma airway inflammation by strengthening

the function of the Transforming Growth Factor (TGF-β) gene by suppressing the expression of the Th-2 cytokines, namely interleukin-4, interleukin-5, and interleukin-13, and eosinophil CC chemokine receptor (CCR3). Piperine has also been stated to be capable of functioning as an immunomodulatory Th-cytokines [110].

3.6. Antibacterial or Antimicrobial activity

Food products should be secured from microorganisms during the storage period to avoid infection. Since there are potential health issues with the continued use of conventional preservatives, consumers are now concerned about their decisions to use modern natural food additives. Spices and herbs have been used by many civilizations to increase the taste and aroma of foods for nations. In addition, they have been used as natural antimicrobials and for the protection of foods [111]. In the prescription of ayurvedic and other conventional medical methods, pepper is most widely used [112].

The natural resistance of plants to bacterial diseases depends on several mechanisms which work at different levels of infection, among which the synthesis of antimicrobial substances is of particular importance. At high concentrations, the antimicrobials isolated so far from plants are active [113]. In 2001, Srinivasa Reddy et al. performed antibacterial action against Gram-positive as well as Gram-negative bacteria in Piper longum isolates. The bacteria that are Gram-positive include Bacillus sphaericus, B. Escherichia coli, Pseudomonas syringae and Salmonella typhimurium are contained in subtilis, Staphylococcus aureus, and Gram-negative bacteria, and piperine was found to be an agent of these bacteria after conducting the experiment [114].

Vanden Berghe et al. used agar diffusion method for the determination of antibacterial activities of the solvent extracts, piperine and piperic acid [115]. In 2018, Hikal D. M. evaluated antibacterial activity of both piperine and pepper oil by using agar well diffusion method against Gram-positive bacteria and Gram-negative bacteria such as Staphylococcus aureus, Bacillus subtilis and Salmonella sp, E.coli, respectively [116].

3.7. Antithyroid Activity

In 2003, antithyroid activity of P. nigrum was assessed by injecting piperine isolated from dried fruits of P. nigrum in albino mice for 15 successive days. Lower concentrations of serum level of both thyroxin and triiodothyronine (thyroid hormones) was reported to be in lower concentrations along with concentration of glucose decrease in hepatic 5'D enzyme and glucose6-phospatase activity. Hence, piperine can be used to inhibit thyroidfunction in euthyroid individuals [117].Vijayakumar et al. reported when piperine administrated in combination with carbimazole, the combination strongly reduced the lipoproteins and plasma lipids, likewise such combination increases the high density lipoproteins level [118]. Singh and Duggal also reported that piperine supplementation significantly reduced thyroid stimulating hormone (TSH) [103].

3.8. Analgesic activity

In 2013, Sabina et al. evaluate the analgesic effect of piperine. For this purpose, it was administered into mice to. Hot plate reaction test and acetic acid test were used and perceived that piperine displays significant analgesic and antipyretic activities without ulcerogenic effects. The results found were comparable with indomethacin (standard drug for reference) [119]. In another study, to determine analgesic activity of piperine in mice, Tail-flick assay and Writhing test were used. Tail-flick test was considered suitable for studying the central mechanism of analgesia. Piperine significantly

increased the tail flick latency (reaction time) in mice similar to morphine, and results of Writhing test was comparable to standard drug indomethacin. Naloxone, an opioid antagonist, eliminated the analgesic effect of piperine and morphine. These results suggest that the antinociceptive activity of piperine is likely to be mediated through opioid receptors. All the researches confirmed analgesic activity of piperine [120]. In 2018, Yasir et al. prepared derivatives of piperine having moieties such as azomethine, sulfamoyl, propanoyl, acetamoyl and heterocyclic oxadiazole and performed analgesic activity of piperine and all the synthesized derivatives for comparative in vivo evaluation of analgesic activity by tail immersion, hot plate and acetic acid writhing methods [121].

3.9. Antihypertensive effect

In 2008, Taqvi et al. stated when piperine administrated intravenously, it possess a Ca^{2+} channel barrier effect which causes cardio-depressant and vasodilator activities, which in turn are the basis for the lowering in blood pressure. It was also reported to have the associated vasoconstrictor effects responsible for the decrease in blood pressure up to a certain limit and a small increase in the blood pressure after decline on administration of dose. Hence, piperine does not allow BP to decrease beyond a certain limit and with fewer side effects [122]. In 2009, Singh and Duggal performed in vitro study on rabbit heart which causes a partial reduction of force, contraction of tissues and blood flow in coronary vessels. Piperine partially inhibited phenylephrine and inhibited high K^+ pre-contractions due to blockade Ca^{2+} channel. In Ca^{2+}-free medium, piperine in low doses exhibited vasoconstrictor effect [103]. In another studies, piperine is also shown to lessen hypertension in N^{ω}-nitro-L-arginine methyl ester hydrochloride (L-NAME) induced hypertensive rat [41, 123]. In 2016, Booranasubkajorn et al. suggested, the mechanism of Thai herbal Sahatsatara formula (STF is a mixed powder of 21 components and piperine is possessed as the most abundant active component of STF) [124-125] and piperine in the vasorelaxation and hemodynamic action may be mediated through the NO pathway. STF and piperine moderately reduced the increase of BP induced by L-NAME administration. Likewise, the pre-treatment of STF and piperine partially restored endothelial-mediated vasorelaxation of aorta that was reduced by L-NAME administration. This is the first study to evidence pharmacodynamics and pharmacokinetics properties, as well as the safety of STF in animal models and provides important and beneficial information for the rational use of Thai herbal Sahatsatara formula in clinical practice [125].

3.10. As Antiasthmatic

Most of the herbal specialists and ancient people believed that asthma reduced by adding crushed peppercorn to green tea [126]. In 2009, Kim and Lee reported that oral administration of piperine in different proportion to mice the production of histamine, immunoglobulin E, interleukin-4, and interleukin-5, which in turn suppressed eosinophil infiltration, airway inflammation, and hyper responsiveness [110]. Additionally, in the piperine-treated group transforming growth factor-b products were improved compared with control groups. Therefore, piperine can be used in the treatment of asthma. Piperine might be capable of acting as a down-regulator of immunomodulatory Th-2 cytokines [110].

3.11. Antidepressant Activity

Li et al. reported, piperine's antidepressant potential was facilitated through the regulation of serotonergic system, while antidepressant action might be mediated via double regulation of both serotonergic and dopaminergic

systems [127]. Tail suspension test and forced swimming tests were used to justify antidepressant activity of piperine as well as its derivative, antiepilepsirine. Wattanathorn et al. also observed the antidepressant activity by the administration of piperine to Wister male rats in different doses ranging from 5, 10 and 20 mg/kg/day for 28 days and finally reported that piperine possessed anti-depression like activity and cognitive enhancing effect during entire treatment duration [128]. In another study, Li et al.[129] and Bai et al. [130] verified its effect on antidepressant activity by using chronic mild stress process in experimental mice. Dosage dependant consumption of piperine used for 15 successive days inverse the chronic mild stress and changes in consumption of sucrose and also plasma corticosterone level. Furthermore, the level of brain derived neurotrophic factor in hippocampus of chronic stressed mice also upgraded by the usage of piperine [103].

3.12. Anticancer activity

Various studies on piperine have been reported that it exhibits anticancer activities both in vitro and in vivo [131-136]. At the molecular level, piperine can influence many effect or proteins engaged in apoptotic process and can activate both intrinsic and extrinsic pathways of apoptosis. Piperine suppressed the tumor development and metastasis in a mouse 4T1 breast tumor model and administration of piperine to 4T1 cells activated caspase 3-mediated intrinsic pathway of apoptosis and induced G2/M phase cell cycle arrest over attenuation of cyclin B1 expression. Significantly, by reducing the expression of MMP-9 and MMP-3, piperine reduced metastatic behavior of 4T1 cells [137]. Another study reported the ability of piperine to inverse the drug resistance of cancer cells in the human cervix. The authors suggested a new therapeutic strategy to enhance the anti-tumor effect induced by mitomycin-C in cervical cancer cells with drug resistance by blocking p-STAT3/p65 and Bcl-2 [138].

The usage of piperine declined the tumor growth in nude mice model xenografted with the androgen independent (LNCaP, DU145) and androgen dependent (PC3) prostate cancer cells. On growth of prostate cancer cells, Inhibitory effect of piperine mediates via reduced expression of phosphorylated STAT-3 and nuclear factor-kB (NF-kB) [139]. Moreover, piperine treatment impaired the expression of androgen receptor (AR) in LNCaP cells. Therefore, piperine can be utilized as a potential chemopreventive agent in the management of prostate cancer. The invasiveness and metastatic behavior of cancer cells is often affected by specific expression of MMP-1, MMP-3, MMP-9, and matrix metalloproteinases (MMPs) and MMP-13 has been related with metastasis and invasiveness of breast cancer cells in vitro [140]. Piperine suppresses phorbol-12-myristate-13-acetate (PMA)-induced MMP-9 expression through its inhibitory effect on protein kinase C-a (PKCa)/ extracellular signal-regulated kinase (ERK) 1/2 activity and inhibition of NF-kB/AP-1 activity [141]. Piperine is also an effective antimetastatic agent against lung carcinogenesis initiated by B16F10 mouse melanoma cells in mice [43] and stifled PMA-induced invasiveness of human fibro sarcoma HT-1080 cells [141]. These studies indicate that piperine is a potent inhibitor of cancer-associated angiogenesis and tumor invasiveness.

3.13. Antiulcer Effect

To check the effects of piperine on gastric ulcers in rats/mice, gastric mucosa damage was induced by stress, indometacin, HCl, and pyloric ligation in rats/ mice and number of gastric ulcers, volume and acidity of gastric juices, and pepsin A activity were identified [142]. Various concentrations of piperine such

as 25, 50, 100 mg/kg used which shows different inhibitory rates for different concentrations, in stress ulcers (16.9%, 36.0%, and 48.3%), in indometacin ulcers (4.4%, 51.1%, and 64.4%), in HCl ulcers (19.2%, 41.5%, and 59.6%), and in pyloric ligation ulcers (4.8%, 11.9%, and 26.2%), respectively. Piperine inhibited the volume of gastric juice, gastric acidity, and pepsin A activity. Therefore, piperine shows antiulcer effect against gastric ulceration [142]. In another study Singh et al. reported, in vivo antiulcer activity was performed [143]. Boddupalli et al. prepared microspheres by using solvent evaporation method and performed in vivo antiulcer activity of prepared microsphere containing piperine. The resultsshows that floating microspheres were able to have good protection against gastric ulcers than other formulations and concluded, the herbal active values similar to piperine can show better antiulcer activities when formulated as novel gastro retentive microspheres rather than the conventional microspheres [34].

3.14. Antifungal activity

The antifungal activity of black peppers volatile oil and its acetone extract against various pathogenic fungi such as Aspergillus flavus (1884), Aspergillus ochraceus (1810), Aspergillus oryzae (1846) Aspergillus niger (2479),Fusarium moniliforme (1893), Fusarium graminearum (2088), Penicillium citrinum (2553), Penicillium viridcatum (2007) Penicillium madriti (3003) and Curvularia lunata (2073) were tested by inverted petriplate [144] and food-poisoning [145] methods. The results of the activities showed positive results towards antifungal property of black pepper [146]. Ertürk et al. performed antifungal activity of ethanolic extracts of Piper nigrum and confirmed its antifungal activity [147].

3.15. Immunomodulatory and antitumour activities

According to some authors, the antitumor activity of piperine is related to its immunomodulatory properties, which involves the activation of cellular and humoral immune responses [148]. In fact, piperine possesses only weak cytotoxic activity [43, 148-150], which indicates that its antitumor activity is not related to direct ant proliferative effects on tumor cells. In 2004, Sunila et al. administered alcoholic extract of Piper longum in addition to piperine and executed immunomodulatory and antitumour activities. Results shows that combination of two inhibit the solid tumor growth in mice induced with DLA cells and upturn the life span of mice bearing Ehrlich ascites carcinoma tumor. Also increased the total white blood cells count, the number of plaque forming cells, and bone marrow cellularity and α-esterase positive cells [148]. In another study, in vivo antitumor activity of piplartine and piperine were estimated in 60 female Swiss mice transplanted with Sarcoma 180. Administration of piplartine or piperine intraperitoneally for 7 days inhibited solid tumor development in mice and the inhibition rates were 55.1 and 56.8% for piperineat the lower and higher doses, respectively [151], in continuation of this, a new study have been done by using both in vitro and in vivo studies to check the effect of piplartine and piperine in combination with the chemotherapeutic agent 5-fluorouracil (5-FU). The incubation of tumor cell lines with 5-FU in the presence of piplartine or piperine produced an increase in growth inhibition, as observed by lower IC_{50} values for 5-FU. Same effects were also observed in in vivo, where the combination with piplartine but not piperine with 5-FU led to a higher tumor growth inhibition [131]. In a study co-administration of piperine and docetaxel resulted in the most significant inhibition of tumor growth among the different experiments. During the experiment none of the mice from group died prematurely. Thus, piperine results in increased docetaxel serum levels, by hindering hepatic clearance of

docetaxel without an increase in docetaxel-mediated toxicities. These findings indicate that piperine may represent a therapeutic strategy to enhance efficacy of docetaxel in treating castration-resistant prostate cancer (CRPC) [77].

4. Conclusion

Use of natural products as medicine has played crucial role in health care of many diseases since ancient times. The scope of natural products is a continuous topic for further exploration.The present review provided an overall description of formulations of piperine and their usage in drug delivery systems.

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