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CHARACTERIZATION AND QUANTIFICATION OF PIPERINE: A BIOACTIVE INGREDIENT OF BLACK PEPPER

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ABSTRACT

One of the most commonly used spices is black pepper (Piper nigrum). For its distinct biting consistency attributed to the alkaloid, piperine, it is appreciated. Black pepper is not only used for human diets, but also for a number of other uses, such as drugs, preservatives and perfumery. In recent decades, several physiological effects of black pepper, its extracts, or its main active ingredient, piperine, have been recorded. Dietary piperine increases digestive ability by favourably enhancing the digestive enzymes of the pancreas and substantially reduces the transit time of gastrointestinal food. In vitro studies have been shown to protect against oxidative damage by inhibiting or quenching free radicals and reactive oxygen species in piperine. Black pepper or piperine treatment has also been shown to lower in vivo lipid peroxidation and to have a beneficial impact on the status of cellular thiol, antioxidant molecules and antioxidant enzymes in a variety of oxidative stress experimental situations. Piperine's most far-reaching feature has been its inhibitory effect on bio-transforming enzymatic drug reactions in the liver. It strongly inhibits hydroxylase and UDP-glucuronyl transferase of hepatic and gut aryl hydrocarbons. In order to improve the bioavailability of a variety of therapeutic drugs and phytochemicals by this very property, piperine has been reported. The bioavailability enhancing property of piperine is also partially due to increased absorption as a result of its effect on the intestinal brush boundary ultrastructure. While there were initially a few controversial reports on the safety of black pepper as a food additive, such evidence was doubtful and subsequent research in many animal studies have proven the safety of black pepper or its active ingredient, piperine. Piperine has actually been shown to have anti-mutagenic and anti-tumor influences, though it is non-genotoxic.

1. INTRODUCTION

In culinary and medicinal preparations, herbs and spices have a longstanding tradition of use. In food production, the delicious taste and health benefits of spices have made them indispensable ingredients. In addition, due to their beneficial pharmacological properties, they have found roles in preparations of various medicines. Among the spices, due to its distinctive pungency and taste, pepper has held a supreme and special role. Black pepper, aptly called the King of Spices, is the most essential and the most widely consumed spice worldwide. It is the only spice invariably eaten at dining tables and is an ingredient in many processed foods that is unavoidable. Black pepper has been used in the past for many reasons, continues to be so now and is predicted to do so in the future.

The importance of pepper is due to its pungence and flavour, which is attributed to the presence of piperine as well as volatile essential oils, a naturally occurring alkaloid. Volatile oils, which make up approximately 0.4% to 7% of black pepper,[1] are responsible for the aroma of pepper, while piperine, as the main constituent of pepper oleoresin, imparts pungent aromas.[2] In plants belonging to the Piperaceae family, the amount of piperine varies; it accounts for 2% to 7.4% of both black pepper and white pepper.[1,2,3] while some studies suggest a higher piperine content of up to 9% of black pepper,[4,5] 4% of long pepper (Piper longum L.) and 4.5% of long pepper (Piper retrofractum Vahl).[4] Many environmental factors can influence the piperine content of pepper, including climate, growing conditions and place of origin.[1]

As the most abundant alkaloid in pepper, piperine was first extracted from pepper extract in 1819 by Hans Christian Orsted. With a melting point of 128 to 130 °C, it was extracted as a yellow crystalline compound. With the chemical formula of $C_{17}H_{19}NO_3$, and with the IUPAC name 1-(5-[1,3-benzodioxol-5-yl]-1-oxo-2,4- pentadienyl) piperidine, the chemical structure of piperine was later known as piperoylpiperidine. Piperine was found to be a very weak base that decomposes into volatile basic piperine, known as piperidine ($C_5H_{11}N$), and piperic acid ($C_{12}H_{10}O_4$)[5] upon acid or alkali hydrolysis. 1-Piperoylpiperidine (piperine) has four isomeric structures: piperine (trans-trans isomer), isopiperine (cis-trans isomer), chavicine (cis-cis isomer) and isochavicine (trans-cis isomer), but there is almost no pungence in the three geometric isomers of piperine.[3]

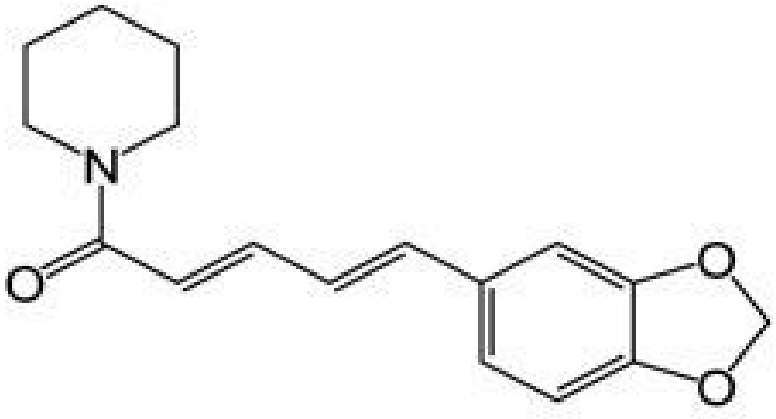
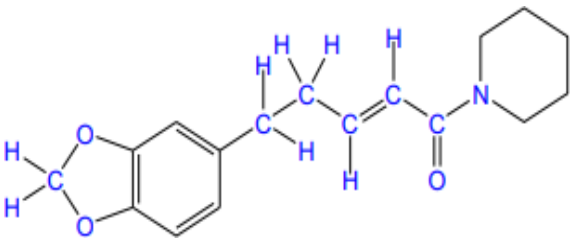
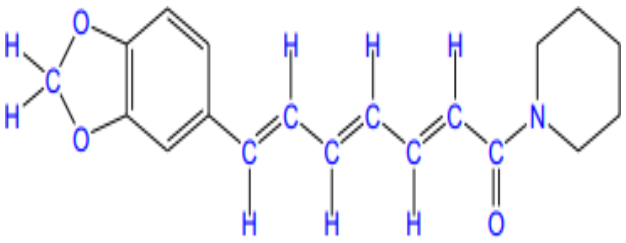


Figure 1: Piperine structure.

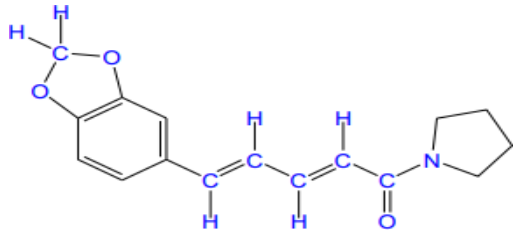
Later studies have shown the presence in the pepper extract of other alkaloids, including piperanine, piperettine, piperylin A, piperolein B, and pipericine, all of which have some degree of pungency. The overall contribution of these alkaloids to pepper pungency was nevertheless found to be negligible. Figure 2 shows the chemical structures of piperine and its analogues.[1,3] Despite debate over the nature of the compounds responsible for pepper pungence, piperine is known to be the main pungent compound of pepper because it accounts for approximately 98% of the total alkaloids in pepper[6] and thus the piperine content is taken as a measure of pepper pungence.[2]



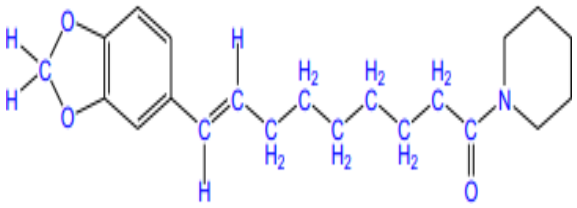
Piperanine



Piperettine



Piperylin A



Piperolein B

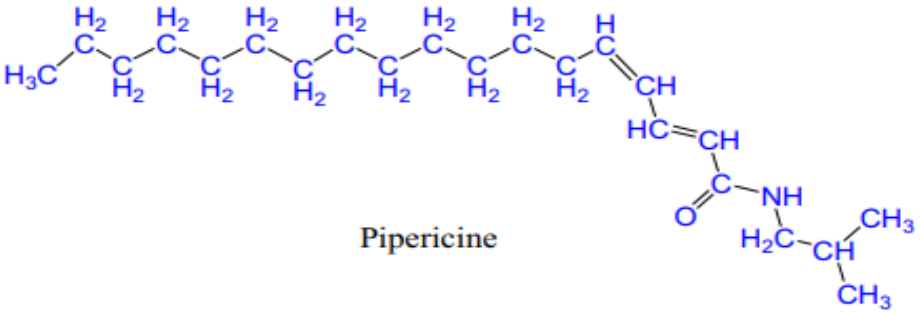


Figure 2: Structure of pipeline's analogs.[42]

2. Thesis Statement

Piperine: For several of the Ayurvedic prescriptions and formulations prescribed for various diseases, piper was primarily included in the formulations as a bioenhancer. Today it is all in practise. Out of 370 drug formulations, 'Trikatu' was one of the ingredients in around 210 drug formulations.[7] Some experiments have shown that 'Trikatu' functions as a bioenhancer for the drugs that surround it. This activity was referred to as Yogvahi by Classics. One of the three ingredients for 'Trikatu' is black pepper. Ginger and long pepper are the other two elements (Piper longum). In allopathic and Ayurvedic formulations, multiple bio-enhancers are currently being applied to different formulations.

Piperine is the active principle of pepper. Piperine is an alkaloid with the $C_{17}H_{19}O_3N$ molecular formula that yields piperic acid and piperidine on hydrolysis. Chemically, piperine is [1, 5-(1, 3 Benzodioxol-5-yl)-1-oxo, 2, 4-pentadienyl], while the piperidine molecular formula is $C_{17}H_{19}O_3NM$. Its pH is 8.6-8.5 and 13.2 pKa. In order to increase its antihistaminic properties, Bose is credited and first describes the value of adding long pepper to vasaka leaves (Adhatoda vasica) and shows that adding long pepper improves the action of vasaka leaves. Atal et al. confirmed the bioenhancer idea put forward by Bose[8] after around half a century.

Piperine had a more sustained reverse respiratory depression action caused by either morphine or barbiturate[9] compared with known analeptic medications such as Metrazol and Nikethemide. Atal researched Piper chaba and proposed that piperine promotes the rapid absorption of co-drugs by either increasing absorption from the gastrointestinal tract or by protecting the drug from being metabolized/oxidized after absorption or by a combination of these two mechanisms in its first passage through the liver.[10]

Consequently, Atal et al.[12] researched the association of piperine with the in vivo and in

vitro biotransformation reaction of hepatic tissue drugs. Aryl hydrocarbon hydroxylation, ethyl morphine-N- demethylation, 7-ethoxy coumarin-o-de-ethylation and 3-hydroxy benzo pyrene glucorodination have been shown to inhibit piperine in rats. The use of Piper longum with drugs like vasicine and sparteine as powder or piperine crystals was found to increase their bioavailability 2.5 to 3.5 times respectively. With 1-oxo- tetrahydrocarbazole and a methylene-dioy-phenyl ring compound, the synergistic effects of piperine and piperic acid were observed.

Oral piperine administration in rats greatly inhibits the glucoronyl transferase activities of AHH (Adenosine hydroxy hydroxylase) and UDP (Uridine di-phosphate). Piperine pretreatment prolongs hexabarbital sleep and paralysis of zoxazolamine in mice. These studies have shown that piperine is a potent drug metabolism inhibitor.[11] In vitro and in vivo regulation by piperine of drug metabolising enzymes was investigated in rat and guinea pig microsomes.[13] These studies have shown that piperine has induced NADPH-dependent cytochrome P- 450 oxidase enzyme concentration-related inhibition, which plays a central role in drug disposal, steady state equilibrium and xenobiotics.

In addition, piperine is a potent UDP-glucoronyl transferase enzyme inhibitor and inhibited the control of the expression of the Cytochrome P-450 1A1 gene in rat heaptoma 5 L cell lines, showing that piperine mediated the impairment of the metabolism of benzo(a) pyrene and, subsequently, the safety of its metabolite- induced toxicity in rat hepatoma 5 L cell culture. This was due to the alkaloid's direct interaction at the post- translation stage with the Cytochrome P-450 1A1 enzyme. The substratum benzo(a)pyrene for the enzyme Cytochrome P-450 1A1 is bio-transformed actively by these cells.[14] Piperine can also interact with the oxidative phosphorylation mechanism, such as activating/deactivating certain metabolic pathways, slowing down drug metabolism and biodegradation.

This piperine activity results in higher plasma levels of the medications, making them more usable for pharmacological action. Oral piperine administration in rats significantly inhibits the glucuronyl transferase activities of AHH (Aromatic hydrocarbon hydroxylase) and UDP (Uridine diphosphate). It has recently been identified that the nerves of NANC (Non-adrenergic non-cholinergic) function independently and cannot be managed directly at will. They are also independent of the nervous system that is adrenergic and cholinergic. Piperine and capsaicin also improve the frequency of the guinea pig's heart rate rhythm. In a group of human volunteers, the metabolism of piperine was studied.

The main piperine metabolites are the 5-(3, 4-dihydroxy phenyl) Valeric acid piperidine. However, it was not possible to detect about 15 percent of the screened individuals.[15] Reen and Singh found that by having a direct effect on vascular endothelium, smooth muscle, and mast cells, piperine enhances the absorption of drugs from the gastrointestinal tract, contributing to improved vascular permeability and mucosal blood flow. Piperine itself is a weak, highly lipid soluble base that resides in the intestinal environment and as an ionised molecule in the stomach in a unionised form. Like piperine, hot spice increases human intestinal epithelial monolayer permeability. Two types of hypotheses exist about the stimulatory impact of the action of gamma-glutamyl trans peptidase (GGT).

One indicates that piperine enhances GGT's affinity to the molecule of gamma-glutamyl-cysteinyl-glycine transpeptidase (GSH), whereas the other expresses a potential altering effect of piperine on the cell membrane phospholipids. This modifying action of piperine, which affects the binding of this membrane-bound enzyme, can increase membrane fluidity. In other words, piperine interacts with the environment of the enzyme and modifies it thereby increasing the activity of the enzyme.[16] The effect of piperine on the metabolic activation and distribution in rats of (3H) AFB1.[17] In a dose dependent manner, piperine markedly inhibited liver microsome-catalyzed (3H) AFB1 binding to calf thymus DNA in vitro. In contrast to the controls, rats pretreated with piperine acquired significant (3H) AFB1 radioactivity in plasma and in the tissues tested.

This effective use of piperine to increase the bioavailability of some medicines has developed interest in the absorption of nutrients and food, as nutritional deficiencies due to poor gastrointestinal absorption are a growing problem in both developing and western countries. A recent bioavailability research has shown that a standardised black pepper extract improves the gastrointestinal absorption of human beta carotene.[17] As a severe side effect, Dapsone, a commonly used antileprosy drug, is known to cause methaemoglobinemia. Based on the recorded interaction between piperine and drug metabolising enzymes, the study was conducted to investigate changes in the bioavailability of dapsone and possible decreases in methaemoglobinaemia in rat piperine presence.

In the presence of piperine in rats, improved dapsone bioavailability increased by up to 62 percent. The bioavailability of structurally and therapeutically different drugs was selectively improved by piperine, either by increasing the absorption rate or by delaying the drug's metabolism or by combining the two processes.[18] Meat, nutrients and xenobiotics are

absorbed through the mucosa of the gastro-intestinal tract. The absorption process in the small intestine is particularly severe. The movement of a compound in the lumen helps to absorb it from the gastrointestinal tract and is part of the mechanism of "biotransformation.

3. The literature review

Pepper piperine isolation Black and white peppers consist of two main components: volatile (essential) oil and pungent compounds, which are responsible for their aroma and pungence, respectively. Pepper oil usually extracted from dried pepper corn by steam distillation, does not contain pungent compounds and represents only aromatic and odorous constituents. Pepper oil is highly regarded in the fragrance industry due to its scent and is used in high-quality toiletries and the perfume industry, as well as in the flavour industry.[19] However, for its pungent and non-volatile compounds contained in the oleoresin of pepper, pepper is highly regarded as a condiment worldwide.

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Generally, an ideal method of extraction should be comprehensive, swift, easy and inexpensive.[20] In certain cases, almost 50 percent to 90 percent of the final product cost is the cost of extraction and purification steps. Choosing an effective extraction method and extraction solvent therefore deeply affects the process economy. Aliphatic and chlorinated hydrocarbon solvent extraction is one of the traditional methods used for piperine extraction.[21]

Nevertheless, these solvents are not piperine-selective and thus, certain major components such as resins and gums are still present in the extract obtained by this process. The purity of piperine should be 95% to 98% for pharmaceutical applications. Therefore, the extract of oleoresin needs further purification with a purity of 40 to 50 percent. Crystallization from aqueous alcoholic solutions and treatment with aqueous alkaline solutions that eventually

minimise piperine production are the most common methods of purification of piperine.[22] Dichloromethane, petroleum ether, diethyl ether.[23,24] alcoholic solvents such as ethanol, hydrotrope solutions, and ionic-based solutions[25] are among the many types of solvents used for piperine extraction.

The typical methods of solvent extraction include soaking, maceration, and extraction of Soxhlet. These methods typically require long extraction times and/or high temperatures, with the possibility of thermal degradation of thermo-sensitive bio-active compounds.[26] In addition, the use of a large amount of solvent and poor selectivity of extraction will contribute to the drawbacks of traditional extraction techniques. In order to mitigate product loss and generate bio-active compounds with unique quality characteristics, such disadvantages have encouraged researchers to look for improved extraction methods.

Modern piperine extraction techniques are supercritical extraction of carbon dioxide (CO_2), ultrasound- assisted extraction (UAE), and microwave-assisted extraction (MAE), which are discussed extensively in the following pages. An overview of traditional and modern methods of extraction is given here; although some of these methods are very capable of extracting piperine with high purity and improved yield, they are still underused and few works have been published in their regard. Figure 2 presents a scheme of separation of piperine from pepper using various methods of extraction.

Soxhlet Extraction There is a long history of using the Soxhlet process to extract useful bio-active compounds. While obsolete, it is still used to assess the efficiency of newly developed extraction methods as the reference leaching technique. A given amount of dry sample is placed in a thimble made of philtre paper for the Soxhlet extraction, which is then placed in a specified distillation device containing the necessary solvent for extraction.

The solvent is heated and the vapour created is condensed, which then drips into the thimble until the overflow level is reached by the solvent. The thimble-holder solution, which carries extracted solutes, flows back into the distillation flask at this time. While the solvent stays in the distillation chamber, the solvent reaches the solid bed again. This method continues until the complete extraction of the bio-active compound.[27,28]

The sample is constantly in contact with fresh solvent in Soxhlet extraction, which accelerates mass transfer and solvent extraction. As another gain, in Soxhlet extraction, the

use of filtration after the leaching process is removed. Although the basic equipment for Soxhlet extraction is easy, a significant amount of solvent is required. Long extraction time, solvent loss, and environmental harm are the most significant drawbacks associated with the extraction of Soxhlet.[26]

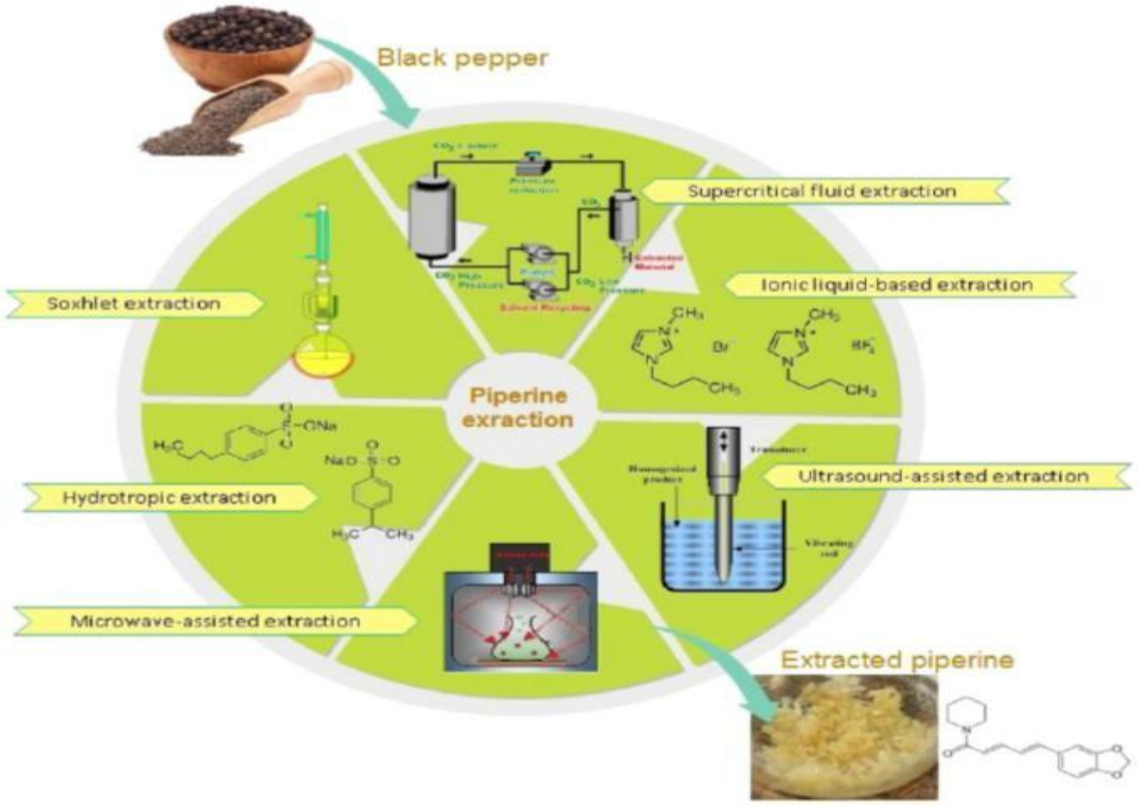

Figure 2: The scheme of piperine extraction from pepper using different methods.

4. Piperine isolation from pepper

Piperine Isotropic Extraction. Hydrotropy refers to the ability of hydrotropes, which are highly water-soluble yet mild surface-active amphiphilic organic salts. The solubility of partially soluble or water-insoluble organic materials in aqueous solutions[29] can be improved by hydrotrope additives. This is due to the tendency of hydrotropic amphiphilic molecules to self-aggregate or to accumulate around other hydrophobic molecules.[30] These accumulations are likely to be much smaller and much less cooperative than micelles of surfactants. Hydrotropes have a major role in destroying the lamellar crystalline structure of surfactants in aqueous solutions, creating a continuous isotropic region of liquid solubility.[31] Compared to surfactants, another defining feature of hydrotropes is their ability to differentiate between the various organic compounds of a mixture, including closely similar substances.[29]

It is this molecular diagnostics capacity that is useful for the enhanced extraction of a drug from crude materials that occur naturally. Great extraction capacities for insoluble organic active compounds can guarantee the high solubilization capacity of a hydrotrope. One that has high water solubility and at the same time, retains its hydrophobicity is a strong hydrotrope. In fact, hydrotropic solubilization is determined by the balance between these two-counteracting characteristics.[32] By disrupting plant cell structures, hydrotropic solutions will remove hydrophobic components from a complex biomatrix. The pericarp of Piper nigrum fruit is made permeable by hydrotrope solutions, thereby simplifying the selective extraction of piperine. This process of extraction can be explained by the potential adsorption of hydrotrope molecules into the cellulosic cell wall, breaking its structure, and then penetrating the cell membrane, helping to disorganize the bilayer of amphiphilic lipids and allowing piperine to be easily released.

Table 1: Different extraction techniques used to extract piperine.

Extraction technique	Extraction time	Extraction yield (w/w)	Benefits	Disadvantages	Reference
Ultrasound assisted extraction (UAE)	18min	0.58%	Shortrunning time, higher extractive yield, controllable parameters	Small particle size, more filtration steps	[43]
Microwave assisted extraction (MAE)	2min	94%	Selective, short running time, high extraction	More filtration steps, time consuming during cooling	[21]
Double bypass Soxhlet apparatus (DBSA)	12±1h	3.90%±0.10 %	Easily operate , simple	Long extraction time, solvent consuming	[44]
Hydrotropic solubilization	2h	90%–96%	Minor purification steps, unlike surfactant not foaming	-	[21]
Supercritical fluid extraction (SFE)	2–5h	6.7%–7.6%	Efficient, selective, clean, fast	gh cost, less pressure resistant	[45,46]
Ionic liquid ultrasound assisted extraction (IL-UAE)	30min	3.57%	Environment friendly, Short extraction run, high efficiency	-	[47]

Hydrotropic piperine extraction Hydrotropy refers to the ability of amphiphilic organic salts called hydrotropes that are extremely water-soluble but slightly surface-active. The solubility of partially soluble or water-insoluble organic materials in aqueous solutions[29] can be improved by hydrotrope additives. This is due to the tendency of hydrotropic amphiphilic molecules to self-aggregate or to accumulate around other hydrophobic molecules.[30] These accumulations are likely to be much smaller and much less cooperative than micelles of surfactants. Hydrotropes have a major role in destroying the lamellar crystalline structure of surfactants in aqueous solutions, creating a continuous isotropic region of liquid solubility.[31] Compared to surfactants, another defining feature of hydrotropes is their ability to differentiate between the various organic compounds of a mixture, including closely similar substances.[29]

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Hydrotropes have a major role in destroying the lamellar crystalline structure of surfactants in aqueous solutions, creating a continuous isotropic region of liquid solubility.[31] Compared to surfactants, another defining feature of hydrotropes is their ability to differentiate between the various organic compounds of a mixture, including closely similar substances.[29] It is this molecular diagnostics capacity that is useful for the enhanced extraction of a drug from crude materials that occur naturally. Great extraction capacities for insoluble organic active

compounds can guarantee the high solubilization capacity of a hydrotrope. One that has high water solubility and at the same time, retains its hydrophobicity is a strong hydrotrope. In fact, hydrotropic solubilization is determined by the balance between these two-counteracting characteristics.[32]

Supercritical piperine fluid extraction Supercritical fluids are commonly used for the extraction of natural materials from compounds. Supercritical fluid extraction (SFE) is a quick, selective, reliable, and clean method for the extraction of natural products, which has recently become very common in the spice and aromatic crop industries. SFE uses solvents with liquid-like densities above their critical temperatures and pressures that cause great solute loading. This makes them ideal solvents for separation and reaction[33,34,35] combined with the pressure-dependent solving ability of supercritical fluids. Kumoro et al.[36] showed that the solubility of piperine in carbon dioxide increased in supercritical and near-critical circumstances, and it was concluded that the increase in solubility of piperine was mainly due to an increase in CO_2 density as well as an increase in strain.

Supercritical fluids are very capable of performing efficient mass transfer, allowing better and faster penetration of desirable compounds into sample matrixes and selective extraction due to their small viscosities and high molecular diffusivity, as well as gases and their small surface tension. Compared to conventional approaches, the most significant downside of SFE is its higher investment costs.[33,38,39] The overall method, however, is almost cost-effective (extraction plus separation) and can be simply scaled up to industrial scale. The most common fluid used for SFE is liquid carbon dioxide (Tc = 31.1 °C and Pc = 73.8 bar) since it is safe, non-combustible, non-toxic, readily accessible, and low-cost.[37] With regard to the use of CO2 as a supercritical fluid, the only downside is that CO_2 has low polarity and may be more suitable for non-polar compound extraction.

However, the addition of chemical modifiers such as alcohol (1 percent to 10 percent of supercritical fluid) to increase the polarity of the solution[40] can overcome this restriction. As an ideal solvent for pepper extraction, supercritical CO2 was used where about 98 percent of piperine and 81 percent of essential oil could be extracted[1] Not only the affinity of the desired and undesired compounds towards extraction, but also mass transfer resistance along the path to the particular position of the desired compound, which depends on the structure of the raw material and can play an important role, should be considered for successful extraction.[34] Another important parameter influencing the SFE yield is temperature. The

solvent strength decreases as the temperature rises due to a drop in supercritical fluid density.[41] In SFE, pressure is the most critical parameter. Increasing the extraction pressure improves the solvent strength but decreases the selectivity of the extraction. The fluid flow rate, particle size of the sample subjected to extraction, and length of extraction[34] are some other effective parameters in SFE.

5. CONCLUSION

Piperine is a significant pepper fruit alkaloid belonging to the Piperaceae family that has a range of medicinal properties. One of them is pepper fruit, which has been formulated for some selected drugs as a bioenhancer. For some antibacterial- antibiotics, piperine has been used as a bioenhancer with positive results. Oxidation, hydroxylation and glucuronidation are responsible for the interaction of piperine with drug-metabolizing enzymes. As it has been used as a bioenhancer for allopathic, Ayurvedic and Unani medicines, piperine appears to be at the top of the list of bioenhancers. Piperine greatly improves the Cmax of various medications. Piperine, pepper's most pungent principle, is an alkaloid with a surprisingly wide variety of therapeutic activities.

It has already been shown to improve nutritional and botanical compounds' bioavailability. In spite of the impressive therapeutic properties of piperine, due to its low aqueous solubility, its pharmaceutical activities have been limited. The low solubility in aqueous environments of this bio-active compound underlines the creation of new approaches that could lead to the sustainable extraction of natural resources, while offering environmentally sound and energy-efficient methods. The advanced techniques used for piperine extraction include supercritical CO2 extraction, ultrasound and microwave-assisted extractions, as well as IL and enzyme-assisted extractions, with certain strengths and advantages over conventional methods, although each process may have its own drawbacks and limitations.

While some studies have been undertaken to extract and purify piperine from pepper, which is needed for biomedical applications, little has been done for the direct use for therapeutic purposes of extracted piperine. The low aqueous solubility of piperine as a drug is the main barrier to its lab-to-clinic development. While some attempts have been made through nano formulations and encapsulation in lipid bodies to improve the bioavailability of piperine, it has a long way to go before it can be used as a medication. The preliminary findings published for medicinal applications of nano formulated piperine are promising and a bright prospect for future therapeutic exploitation of piperine can be anticipated due to recent

developments in the field of biotechnology.

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