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Possible Effectiveness of Piperine against Biological Problems

Mohd Zeeshan*[1], Archana[2], Smita[3], Gopal Rai[4]
[1,2]*Saroj Institute of Management, Lucknow U.P India*

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ABSTRACT:
Piperine is an important target agent for the development of potent antioxidants. This heterocyclic nucleus's planar nature makes it possible to incorporate acetamide groups at different ring configurations. The Piperine heterocyclic has attracted a lot of attention in the field of pharmacological discovery. The wide range of its therapeutic applications opened the door for researchers to occasionally implant the nucleus in varied pharmacophores to develop a new therapeutic profile. In this article, we have made an effort to summarise several clinical applications that the experts have already clarified. The study will assist the researcher to create scaffolds with the maximum efficacy of treatment, given the significance of the Piperine nucleus. We also provided examples of the various Piperine types and their origins in Pinus plants.

Keywords: Pinus, plant, Piperine, anticancer, pharmacological,

I. INTRODUCTION:

The widely called longleaf Indian pine is a giant planthavinga large canopythat exists normally throughout the Himalayas from Jammu- Kashmir to Afghanistan, &in the hills of South India. Often it is grown for ornamental practices in the garden (Shuaib, M., and et.al. 2013).The species have endless needles as well as a long lifetime, that's why there is a strong request in respect of protection towardsdifferent, biotic & abiotic harass. Therefore broad phenolic chemical verities, like condensed tannins,stilbenes& acetylated flavonoids, andterpenoid resins, have rich protective chemistry (Zhao et al., 2011;Strack et al., 1989; Virjamo, V.et.al., 2013). Furthermore, this genus synthesizes alkaloids, 2, 6-disubstituted Piperine(Tawara et al., 1993, Stermitz et al., 1994). To our awareness, P. sylvestris alkaloids were rarely quantified or from plant parts apart from needles.In the history books of human and livestock toxicity, Piperine alkaloids with a distinctive condensed heterocyclic ring configuration hold a special position. (Fig. 1) maybe the first unusual case of part of this category of alkaloid poisoning was indeedthe assassination of philosopher Socrates in 399 BC. (Lee, S. T., et.al. 2008). The philosopher swallowed Conium maculatum, a plant comprising elevated c-coniceine (1) and amounts of coniine (2), referring to the popular account by Plato in Phaedo (Reynolds, 2005Agatha Christie pursued this trend in common literature in a tale plot that included a poisonous hemlock extract said to be high in coniine (2) as a way of murdering her novel Murder in Retrospect (1984). (Hagiya et al., 2010;Gehlbach et al., 1974Schep et al., 2009).

The most common conifer genus currently extant has over 100 generally known species, and its family name is Pinaceae (Farjon, 2001). In Taiga, temperate, subalpine, and tropical forests as well as dry woodlands, pines form a prominent, occasionally dominant component (Gernandt et al., 2005). Pines are a vital resource of timber, resin, paper, charcoal, edibles (including seeds), and ornamentals in the commercial world (Gernandt et al., 2005). Except for one population of P. merkusii, located just south of the equator in Sumatra, the genus is only found in the northern hemisphere (Gernandt et al., 2005).Globally, cultivated species include P. patula, P. caribaea, P. radiata, P. pinaster, and P. radiata (Gernandt et al., 2005). Before updating the evolutionary history of pines, Price & colleagues (Price, 1998) (Price, 1998) presented data from morphology, cytology, crossability, anatomical, secondary metabolites, proteins, and DNA comparisons. There are various ethnomedicinal uses for drugs made from Pinus species worldwide. They are employed as tonic, antiseptic, and expectorant, especially in urinary and respiratory system disorders, and externally used in skin disease. Additionally, P. pinea, P.sylvestris, and P. nigra have antimicrobial activities (Kızılarslan & Sevg, 2013).

Numerous studies have examined the chemical makeup of Pinus(P. halepensis Mill.) extracts and essential oils that grow in various regions of the globe. According to the section of the plant that was used and the location where the samples were taken, different essential oils and preparations of P. halepensis Mill. have different

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chemical compositions.Terpenoids are the most prevalent and active category of secondary metabolites in P. halepensisMillessential .'s oil and extracts. Chromatographic and spectroscopic methods helped isolate and identify several fatty acids and steroids from P. halepensisMill .P. halepensis Mill. Seed oil from Brazil, which was obtained using 405 hexane, has a chemical makeup that was high in fatty acids (El Omari et al., 2020).

Certain literature elaborated on the chemical constituents of extracts and essential oils of pinus (P.halepensis mill.) developing in various parts of the word. The chemical constituents of essential oils and extracts of P.halepensis mill. Alters on basis of plant parts employed and where the samples were obtained. Terpenoids are an abundant and functional group of secondary metabolites in essential oils and extracts of pinus species speciallyP.halepensismill,Spectrophotometric and chromatographic techniques helped in the isolation &identification of certain fatty acids and steroids from essential oils and extracts of pinus. The chemical constituents of P.halepensis mill. Seeds oils isolated with hexane were enriched in fatty acids (El Omari et al., 2020).

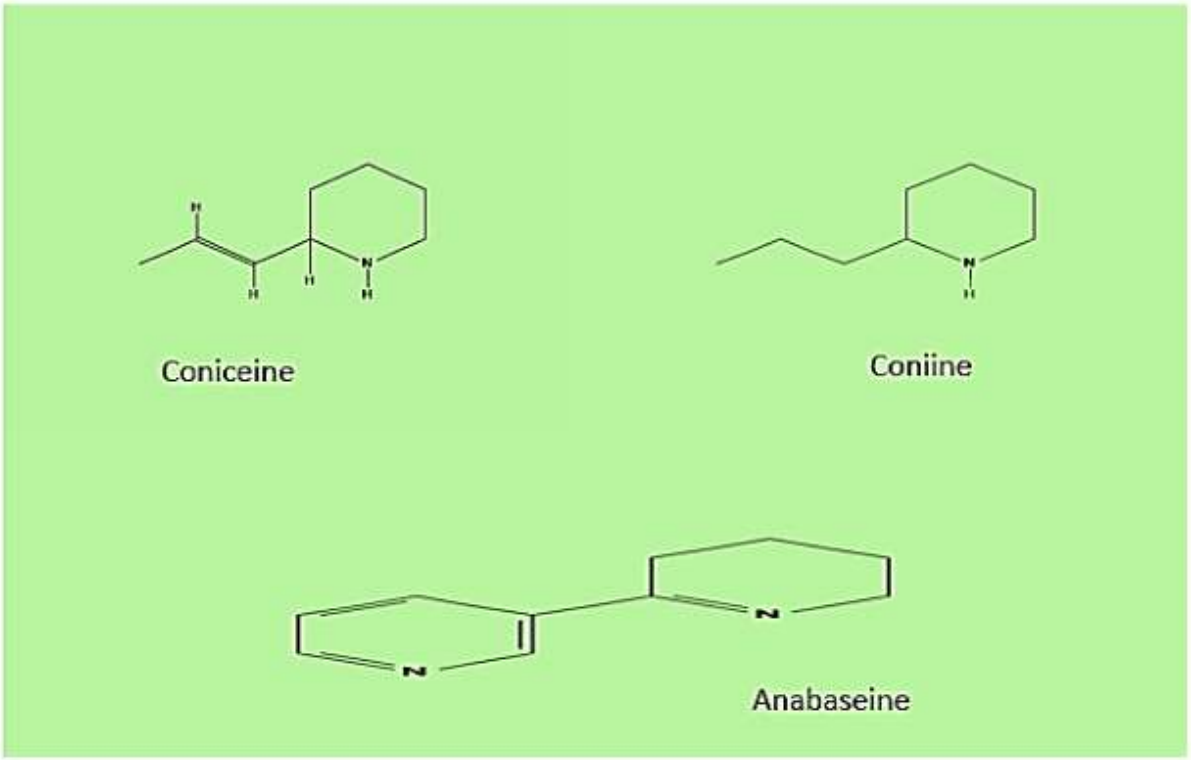

Fig 1. Alkaloids with a distinctive condensed heterocyclic ring. (A) Coniceine (B) Anabaseine (C) Coniine.

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Fig.Some important Piperine derivatives.

There is some naturally occurring Piperine present in nature that is summarized in table 1:

Alkaloid	**Molecular formula**	**Molecular weight (**g/mol)
(+)Epidihydropinidine:	$C_9H_{19}N$	141.25
(+)-6-Epi-9-Epipinidinol	$C_9H_{19}NO$	157.25 g/mol
(-)-Pinidinone	$C_9H_{17}NO$	155.24 g/mol
(+)-Euphococcinin	$C_9H_{15}NO$	153.22 g/mol
Prosopinine	$C_{16}H_{33}NO_3$	287.44 g/mol
Piperine	$C_{17}H_{19}NO_3$	285.34 g/mol
Sedamine	$C_{14}H_{21}NO$	219.32 g/mol
Adaline	$C_{13}H_{23}NO$	209.33 g/mol
Histrionicotoxin	$C_{19}H_{25}NO$	283.4 g/mol

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Natural Sources of Piperine and their and function:

One of the major classes of alkaloids is Piperine alkaloids, which have been the topic of different reviews(Fodor, G. B., &Colasanti, B. (1985), Strunz, G. M. (1986),). Piperine itself is a natural product produced by plants such as Piper nigrum L., Piperaceae, and alkaloids ofPiperine are categorized on basis of its common resource. It is possible to categorize Piperine alkaloids based on their composition, fused-ring Piperines 2,6-cis-Piperine:2,6-trans-PiperinePiperinessteroidal

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Piperines,1-acetylPiperine, alcohols containing Piperine, and so on. Prosopinine has been isolated from ProsopisAfricana Taub leaves, stems, and roots(Fodor, G. B., &Colasanti, B. 1985), and has a broad range of biochemical functions, such as hypotensive, sedative, local anesthetic, spasmolytic, antiseptic, etc. Piperine24ID has been extracted from the skin of Dendrobates speciesdart-poison frog (Edwards, M. W., et.al., 1988) and inhibits the action of acetylcholine by non-competent nicotinic receptor-channel complex blockade (Daly, J. W., et.al.1991). Piperine, extracted fromPiper nigrum(black pepper), has many pharmacological functions, such as a boost in the Intestinal epithelial cell permeability as activation of the pituitary-adrenal axis cells, and dopamine p-hydroxylase inhibition (Huang, C. G., 2002). Sedamine was extracted from Sedum acre (Marion, L., Lavigne, R., & Lemay, L. (1951) and was observed Pea diamine oxidase inhibition competitively (Peč, P., &Frébort, I. 1991). Adaline is a protective alkaloid extracted from Adaliabipunctata (Brown, W. V., & Moore, B. P. 1982)., the European two-spotted ladybug. The histrionic toxin isone of the components of Dendrobate frogs' protective secretions of skin thatserves as venom and also an irritant to the mucosal tissue of mammals and reptiles(Daly, J. W., et.al., 1987). It is suspected that this alkaloid blocks the complex ofthe nicotinic receptor channel (nAChR) and inhibits the binding positions in the Na, K, and Ca channels Membranes in the brain (Lee, S. T., et.al.2008).

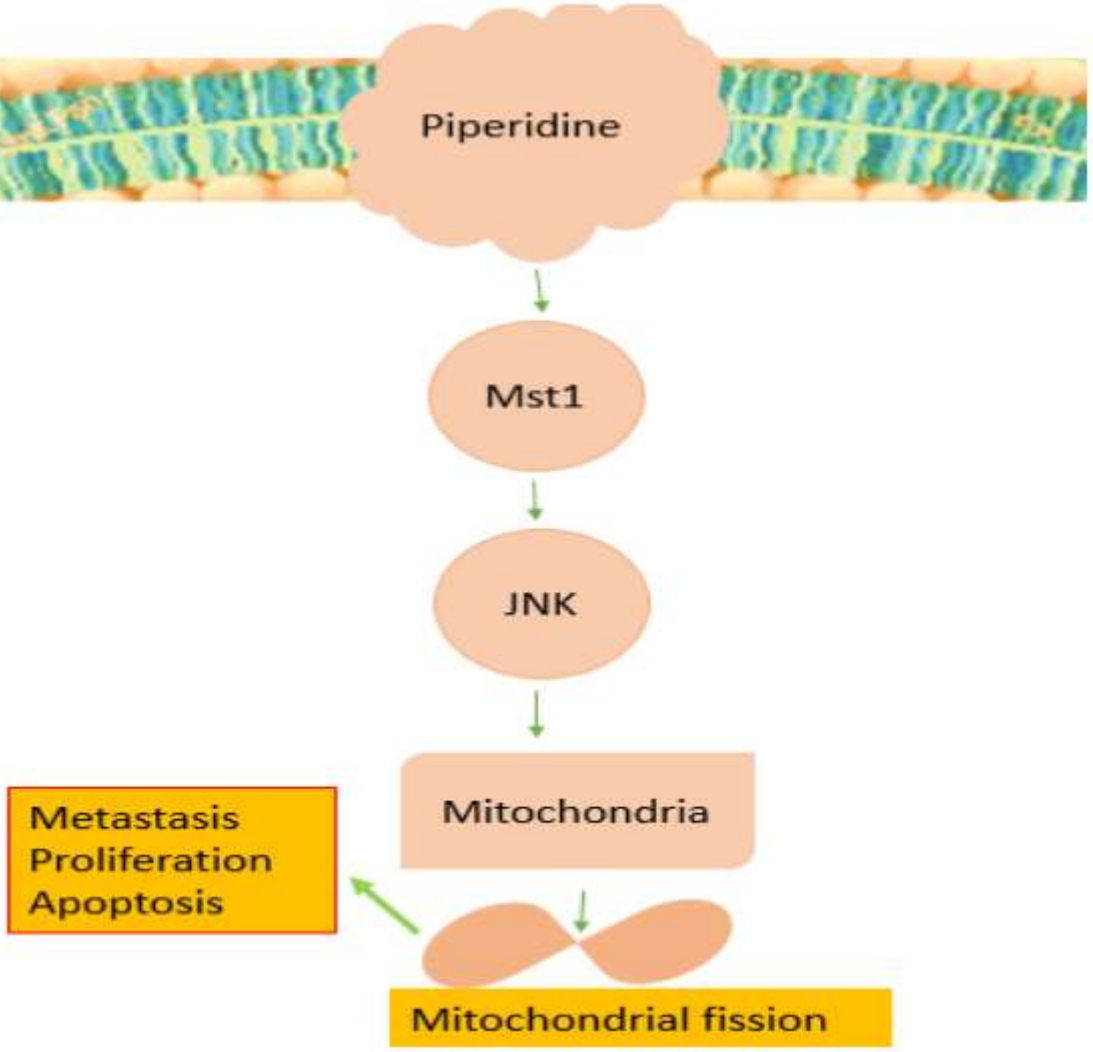

Fig2: The main process of Piperine alkaloid toward liver cancer

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Piperinefrom pinus species

The first alkaloid obtained from conifer species was called alpine-pipecoline, a meaningless name that was later given to the alkaloid as pinidine (Tallent et al., 1955). The components and full structure of the pinidine are computed as 2R-methyl6R-(2E-propenyl)-Piperine(Hill et al., 1965, Tallent and Hornig, 1956). Since several additional Piperine-related alkaloids from Pinus and Picea species have been discovered (Schneider and Stermitz, 1990).

In contrast, spruce plants contain both cis- and trans-Piperine alkaloids, whereas pines tend to produce primarily cis-Piperine alkaloids (Schneider et al., 1991). A handful of the well-known alkaloids from spruce and pine also have been found in insect species. For example, the Mexican bean beetle Epilachnavarivestis produces dihydropyridine and euphococcinine. Most likely, euphococcinine serves as a secondary metabolite that keeps predators at a distance (Eisner, E. et al., 1986).(+)-Dihydropyridine Hydrochloride Salt was used in experimental analysis. The pine weevil was targeted by antifeedants with high activity (Schlyter et al., Results Unpublished). Such a solution might also be suitable for use in protecting new Pinophyta from pine weevil feed. The substance was discovered in the needles of Piceapungens (Todd, F. G. et al., 1995) as well as in the bark and needles of Piceasitchensis (Gerson, E. A., & Kelsey, R. G. (2002).The structure of the substance in these organisms does not, however, have been mentioned to be.

TABLE 1: Some common Piperine alkaloids present in pinus species.

S.N.	Name of alkaloid	source	References
1	(+)-6-Epidihydropinidine	P. abies and P. pungens	Tawara, J. N. et.al.,1993
2	(+)-6-Epi-9-epipinidino	P. abies and P. pungens	Tawara, J. N. et.al.,1993
3	(-)-Pinidinone	P. pungens	Tawara, J. N. et.al.,1993
4	(+)-Euphococcinine	P. edulis	Tawara, J. N. et.al.,1993
5	(+)-l,2-Dehydropinidinol	P. nigra and P. syluestris	Tawara, J. N. et.al.,1993
6	Piperine	Piper nigrum and Piper longum	Hamrapurkar, P. D., et.al.,2011.
7	Sanguinarine	Sanguinariacanadensis L. and Chelidoniummajus	Croaker, A., King, G et.al., 2016

Piperine alkaloid genetic variation in Pinus:

Pinus ponderosa provides a variety of Piperine alkaloids in the majority of tissues (Tallent et al., 1955). One of the common and secure end products (pinidine) in mature leaves is produced by a variety of processes and intermediates during the biosynthesis process (Leete, E., & Juneau, K. N. 1969). According to an exploratory research effort on Pinus ponderosa, alkaloid heterogeneity due to cumulative genetic and environmental impacts is based locally to the extent that alkaloids can be missing (Gerson, E. A., & Kelsey, R. G. 1998).Environmental influences on ponderosa pine alkaloids were documented in a field fertilization analysis, showing the ability of nitrogen availability to influence alkaloid variation (Gerson and Kelsey, 1999a). Similar to secondary metabolite molecules with a 9-carbon atom-1-nitrogen atom structure, the formation of alkaloid Piperine can include tradeoffs for tissue growth and functions (Stamp, 2003).

The significant differences in alkaloid levels between regions in ponderosa pine have shown extensive intraspecific genetic variability. An analysis by Gerson, E. A., et al., 2009 found that the Columbia River Gorge had the lowest overall average concentration of alkaloids and the Northwest stage region of Fort Lewis had the highest. Although the alkaloids in such two regions were the most different, they are geographically close to one another.

In general, there was a significant difference in the levels of alkaloids in the western provinces (WV, FL, & MN) and the eastern provinces. It is crucial to first look into the developmental history of Pinus ponderosa in North Western USA to comprehend such a significant biochemical difference across such a broad geographic area. Since it is most frequently found in the Picea and Pinus genera, which are regarded as being somewhat primitive in the phylogeny of the Pinaceaeae, the creation of Piperine alkaloids appears to be an evolutionary trait (Wang, X. Q. et al., 2000). Variability in this trait could be a sign of relocation, geographic proximity, genetic evolution over time, as well as a response to environmental factors.

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The biological activities of Piperine:

The Piperine-derived alkaloids are typically isolated from Conium maculatum L. as well as Piper nigrum L. Plants. It is projected that work has been carried out on 700 participants of this class. These polyphenols are aware of their potency and have a saturated heterocyclic ring (Piperine nucleus).These have many antibacterial, anticancer, antidepressant, anti-histaminic, herbicidal, CNS stimulant, fungicidal, andinsecticidal pharmacological activities (Herman, A., & Herman, A. P. 2013).

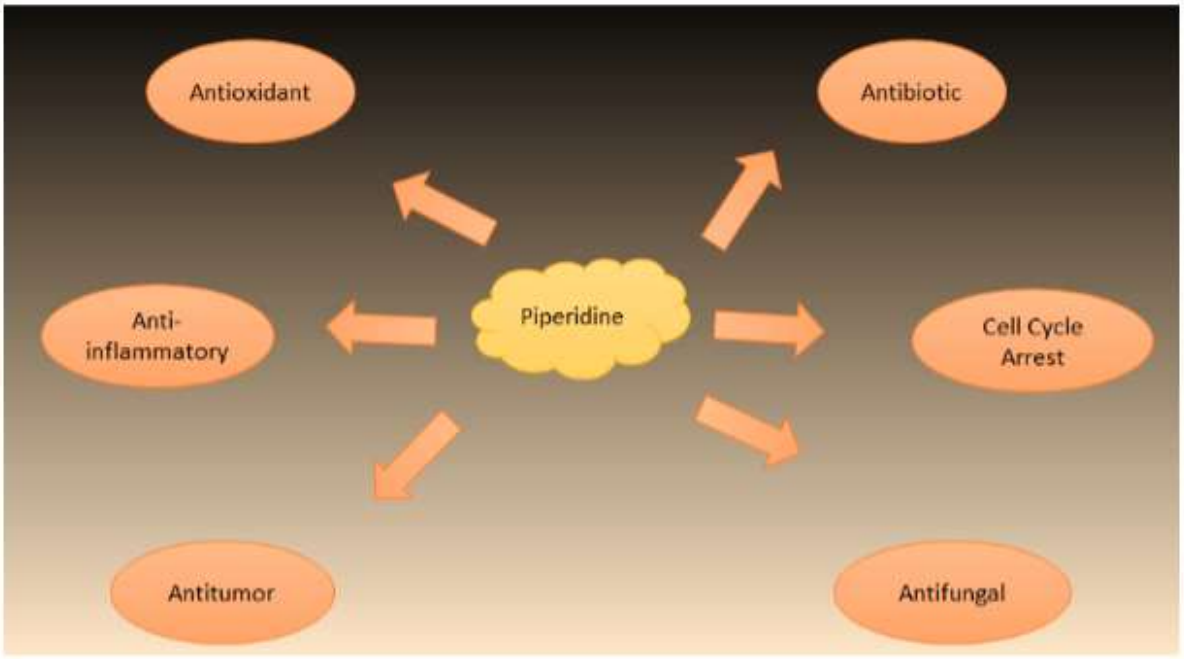

Fig 1: Biological activity of Piperine.

The Piperine alkaloids produce the popular hemlock poison known as Conium maculatum. Coniine, Lobeline, & cynapine are part of the alkaloids ofPiperine. Alkaloids of Pyridine have a very similar structural framework to that of alkaloids of Piperine, except for the unsaturated bonds in their nucleus that are heterocyclic. Some of the pyridine alkaloids are anatabine, anatabin, anabasin, nicotine, and epibatidine(Dhar S áYadav, L. 2012). Piperine is an alkaloid of Piperine which exists in Piperlongum and Piper nigrum (Szallasi, A. 2005). Additionally, itis a catalyst for the development of bile secretion (Yadav, V. et.al. 2020, Srinivasan, K. 2007). and a CNS system suppressant,it displays antidiarrheal, antioxidant, anticonvulsant, anticancer anti-inflammatory, and antihyperlipidemic activity (Lee, S. A., et.al.,2007). Strong tumor size in rodents grafted with sarcoma 180 cells was significantly reduced by administering100 mg/kg or 50 mg/kg of piperinefor a week regularly. Previously, a report has shown thatpiperine has selectively prevented the development of cancerinthe breast (Antalis, C. J et.al. 2010). This secondary metabolite has been observed to cause a stopping point in the cell division cycle in the G2-M transition stage & apoptosis in cells of 4T1 (Lai, L. H.,et.al., 2012). Piperine is also effective toward lung cancer metastases triggered by B16F-10 melanoma cells in mice at a dose of 20 μM/kg(Pradeep, C. R., &Kuttan, G. 2002) and induces repression of 12-O-Tetradecanoylphorbol-13-acetate which induces invasion of tumor cells (Hwang, Y. P., et.al., 2011).

NF-nB, proton oncogene, CREB (cAMP response element-binding), and ATF-2 (enabled transcription factor 2) (Pradeep, C. R., &Kuttan, G. 2004) are inhibited by piperine. It represses the expression of PMA-induced MMP-9 by inhibiting PKC alpha/ ERK 1⁄2 and reducing activation of NF-B/AP-1 (Hwang, Y. P., et.al. 2011). Piperine also prevents CYP3A4 and P-glycoprotein (P-GP) activity, which influences the metabolism of drugs and also re-sensitizes cancer cells immune to multidrug (MDR) (Bhardwaj, R. K., et.al.,2002, Li, S., et.al.,2011). Piperine improves the efficacy of docetaxel by suppressing CYP3A4, which is the key metabolizing enzyme of docetaxel, without

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causing further side effects on the treated mice (Makhov, P., et.al. 2012).

Table 3: Summarization of activity of Piperine Alkaloids

Piperdine	Activity	References
oxyl or oxidanyl	Antioxident	Ali, B. M.,et.al.,2020
TEMPOL	Antioxident	Francischetti, I. M., et.al., 2014
f 3, 4, 5-trisubstituted Piperines	Antioxidant	
iso-6-cassine	Antioxident	Freitas, R. M. D.,et.al.,2011
Phenylcyclidine (PCP)	Antioxident	Lin, C. H., ET.AL., 2020
2-hydroxy Pyrrolidine	Antibiotic	Bhola, Y. O., &Naliapara, Y. T. (2019)
Piperine	Immunomodulator and Antitumor	Ferreira, R. C., et.al., 2020
Benzophenanthridine	This causes many cancer cells to undergo apoptosis or the cell division cycle to cease.	Zhang, B., et.al.2019
Tetrandrine	Depending on the kinds of cancer cells, different cell cycle detention phases can be induced.	Yu, B., et.al., 2020
6-Epidihydropinidine	antibiotic	Fyhrquist, Pet.al., 2019
piperidin-4-one oxime	Excellent inhibitory efficacy against S. faecalis and P. aeruginosa.	Thirunarayanan, G., &Lakshmanan, K. (2019).
piperidin-4-yl-5-spirothiadiazolines	good inhibitory effect against different types of microbial strains, like S. aureus (ATTCC-25825), S. Typhi (ATCC-24915), B. subtilis (ATCC- 451), K. pneumonia (ATCC-15490), E. coli (ATCC-25835)	Ghatpande, N. G., et.al.,2020
3-benzyl-2, 6-diarylPiperine- 4-one	Activity against various bacterial and fungal strains.	
1,3,5-Triazine	Anti-mycobacterial, potential anticancer agents.	
N-(Nmethylpiperazinoacetyl) -2, 6-diarylpiperidin-4-one	possessing good antimicrobial, antipyretic, and analgesic effect	
7-(4-alkoxyimino-3-amino-3-methylPiperine-1-yl)fluoroquinolone	Good anti-bacterial activity.	Ghatpande, N. G., et.al.,2020
3, 5-bis (benzylidine) piperidin-4-one	Suppressing activity against several types of malignant cell lines, HSC-2, and HSC-4.	
3,5-bis(pyridin-2-ylmethylidene)piperidin-4-one	Good anti-cancer, anti-inflammatory property.	
dispiro[3H-indole -3, 2'-pyrrolidine-3', 3''-Piperine] -2(1H), 4''-dione	exhibited good anti-tumor and anti-inflammatory activity.	
piperidinyl pyridine	Inhibitory activity against IKK-ß	

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	is one of the possible targets of cancer.	
1-(2-((Z)-6-(2-(Trifluoromethyl)phenyl)hexa-3-en1,5-diynyl)phenyl)-piperidin-2-one	New potent apoptosis agent.	
piperidin-4-yl-aminopyrimidine	Activity against first-generation NNRTI resistant mutant virus.	

II. CONCLUSION:

It has been demonstrated that the plant compound Piperine, which is extracted, provides advantages for both people and animals. Investigations into a variety of these alkaloids have revealed that a significant number of them use a range of pharmacological strategies. These activities are a part of antibacterial, anticancer, antiviral, antifungal, and antioxidant programs. . However, when high amounts of piper dine are consumed, hazardous effects might be seen, and in some circumstances, deaths are unavoidable. For instance, it has been demonstrated that some alkaloids can sometimes cause death, paralysis, or suffocation. To create medications that are more potent, less poisonous, and more resistant to different bacteria, research has been conducted over the past few years to create new derivatives of the Piperine alkaloid. The development of novel effective medications based on external products is expected to proceed more quickly and profitably if modern methodologies, state-of-the-art technologies, and statistical approaches are combined.

Many plants have poisonous secondary metabolites that, when released, can endanger humans. However, the instances of lethal plant poisoning are very rare. The most severe poisoning accidents are those involving the use of herbs for hallucinogenic purposes. Evaluation of toxicity or assault instances may be aided by using toxicity tests of such secondary metabolites. Coniine is one of the dangerous piperdine metabolites, and it frequently causes fatal poisoning (Salehi, B., et.al.,2019).

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