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DRUG LIKENESS AND PHYSICOCHEMICAL PROPERTIES EVALUATION OF THE ALKALOIDS FOUND IN BLACK PEPPER: PIPERINE, PIPERIDINE, PIPERETTINE AND PIPERANINE

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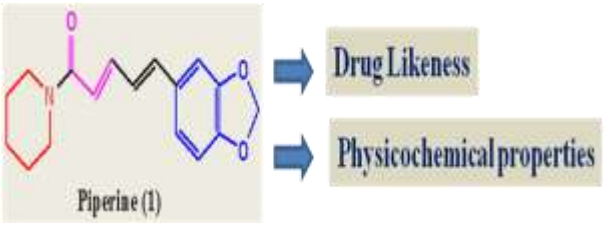
ABSTRACT

The alkaloids found in black pepper 1-4 were evaluated for their drug likeness and physicochemical properties using Lipinski's rule of five and Molinspiration (web based software). The results of computational studies revealed that all alkaloid were found to possess good bioactivity score except piperidine. It indicates that only the combination of all these three functionality (the piperonal nucleus, piperidine nucleus and the presences of α-β-unsaturated ketonic group) is responsible to exhibit biological activity. To study the biological activity of black pepper extracts, piperine and its derivatives have been long targeted by researchers and still aimed. Our study will help researchers for further developments with black pepper alkaloids.

KEYWORDS: Black pepper alkaloids, drug likeness and physicochemical properties.



1. INTRODUCTION

Black pepper (Piper nigrum Linn.) is a flowering vine of Piperaceae family. It is native to India and has been a prized spice since ancient times. Black pepper has versatile biological application and is used to treat vertigo, asthma, chronic indigestion, colon toxins, obesity, sinusitis, congestion, fever, paralytic, arthritic disorders and also advised in diarrhoea and cholera.[3-5] Piperine is considered as the major plant alkaloid found in black pepper (*Piper nigrum*) and long pepper (*Piper longum*), is reported to have bioavailability-enhancing activity for some nutritional substances and for some drugs.[1-3] Piperine, is easily isolated from grounded black pepper as the black pepper is composed of 5-9% of alkaloids including piperidine, piperettine and piperanine and comes from the dried fruit of aschanti **Figure-1.** The extracts of black piper is widely investigated as anti-apoptotic, Antibacterial, Anti-Colon toxin, Antidepressant, Antifungal, Analgesic, Antidiarrhoea, Anti-inflammatory, Antimutagenic, Anti-metastatic activity, Antioxidative, Antiriyretic, Immuno-modulatory, Antispasmodic, Asthma, obesity, sinus, Antispermatogenic, Antithyroid, Antitumor, Ciprofloxacin potentiator, Colic, Cold extremities, Gastric ailments, Hepatoprotective, Increase plasma, Increase pancreatic enzymes, Inhibit cytochrome, Inhibit transcription, Insecticidal activity, Intermittent fever, Larvisidal activity, Pesticidal activity.[6-58]

On the other hand the enormous research has been done on the naturally occurring piperine piperine and modifications on piperine which exhibits that piperine and its derivatives are found possess potential anticancer, anti-inflammatory, thermogenic, growth stimulatory, anti-thyroid and chemo preventive activities, antipyretic, analgesic, insecticidal, immunomodulatory, antitumor, anti-depressant and anti-apoptotic activities, inhibition of hepatic drug metabolism, enhancing pentobarbitone induced hypnosis, bioavailability of oxyphenyl butazone, hepatoprotective, inhibition of lipid peroxidation during experimental inflammation, antifertility, and radio protective effects and many others properties.[59-87]

There are three components in the structure of piperine (Piperidine, piperonal nucleus and α, β-unsaturated ketone functionality). The piperonal nucleus itself is found in a number of biologically compounds occurring naturally as well as synthetically. The enormous biological applications of piperine, prompted to evaluate some parameters such as drug likeness and physicochemical properties with respect to piperine.

2. EXPERIMENTAL

Lipinski's rule of five[88-91]

Lipinski's rule of five states that, in general, an orally active drug has not more than 5 hydrogen bond donors (OH and NH groups), not more than 10 hydrogen bond acceptors (notably N and O), molecular weight under 500 g/mol, partition coefficient log P less than 5, number of violation less than 4. Physico-chemical properties of alkaloids 1-4 were checked with the help of software Molinspiration physicochemical prpperties calculator available online (www. molinspiration.com). The properties which are calculated are partition coefficient (log P), molar refractivity, molecular weight, number of heavy atoms, number of hydrogen donor, number of hydrogen acceptor and number of violation.

Bioactivity score[89-91]

The drug likeness for alkaloids 1-4 were also checked for GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand. All the parameters were checked with the help of software Molinspiration drug-likeness score online (www. molinspiration.com).

3. RESULTS AND DISCUSSION

Physico-chemical properties and drug like ness of alkaloids 1-4, **Figure-1** were checked with the help of software Molinspiration physicochemical prpperties calculator available online (www. molinspiration.com). The properties which are calculated are partition coefficient (log P), molar refractivity, molecular weight, number of heavy atoms, number of hydrogen donor, number of hydrogen acceptor, number of violation, GPCR ligand, ion channel modulator, kinase inhibitor and nuclear receptor ligand and the results are reported in **Table-1 and Table-2.** Results revealed that all the alkaloids found in black pepper follows the Lipinski's rule of five and all have good bioactivity score except piperidine.

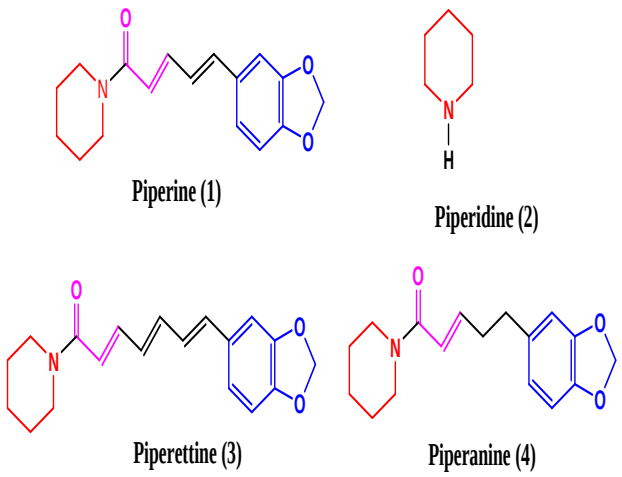


Figure-1: Representing the structures of alkaloids present in black pepper

Table-1: Physicochemical properties of all the alkaloids present in black pepper

Physicochemical property score	Alkaloids			
	1	2	3	4
miLogP	3.332	0.66	3.85	3.59
TPSA	38.777	12.03	38.78	38.78
Natoms	21.0	6	23	21
MW	285.343	85.15	311.38	287.36
nON	4	1	4	4
nOHNH	0	1	0	0
Nviolations	0	0	0	0
Nrotb	3	0	4	4
Volume	267.741	98.20	295.16	273.93

Table-2: Drug likeness of all the alkaloids present in black pepper

Bioactivity score	Compounds			
	1	2	3	4
GPCR ligand	0.15	-3.39	0.18	0.18
Ion channel modulator	-0.18	-3.30	-0.17	-0.07
Kinase inhibitor	-0.13	-3.75	-0.08	-0.12
Nuclear receptor ligand	-0.13	-4.10	-0.07	-0.07
Protease inhibitor	-0.10	-3.43	-0.03	0.01
Enzyme inhibitor	0.04	-3.51	0.03	0.10

4. CONCLUSION

All the alkaloids 1-4 found in black pepper were subjected for computational studies to calculate the drug likeness and the physicochemical properties. All the alkaloids follow the Lipinski's rule of five, but in case of drug likeness, only the alkaloids piperine, piperettine and piperanine were found to have good bioactivity score which means that these alkaloids can be used as lead compounds for versatile biological application. The black pepper extracts, piperine and its derivatives have been widely investigated by the researchers and still the researchers are attracted to this field. Our study will provide researchers a platform for further developments with black pepper alkaloids.

5. Conflict of interest

The authors have no conflict of interest.

6. ACKNOWLEDGEMENT

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