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Black Pepper, Dietary Photochemicals in the Prevention of Diseases by Oxidative Stress (A-Review)

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ABSTRACT

Medicinal plants are widely valued and are of prime concern globally. Scientific exploration on the flora and fauna of the globe increased, identifying drawbacks in synthetic utility of drugs like poor absorption, high dose, low bioavailability, and poor patient compliance. Plant based pharmaceuticals are considered as an alternative therapy and phytochemicals are being approved as drugs. Our interest is to explore on the spice, Black pepper which is classified under safe herb by FDA. The literature studies are collected estimating the efficacy of the spice against a variety of disease conditions like asthma, diabetes, hyperlipidaemia, inflammation, cancer, oxidative stress, gastrointestinal secretion, lipid metabolism, etc. In this review, we focussed on the scavenging capacity of black pepper in the abduction of free radicals. Increased in the production of free radicals is linked to causing oxidative stress in the body which is underlying cause for many lifestyle disorders like obesity, diabetes, congestive heart failure, myocardial ischemia, and different forms of cancer such as breast, prostate, lung, endometrial, skin, stomach, etc. This review focuses on the efficacy of black pepper and its relationship with many diseases.

Keywords: Black pepper, Natural medicine, Plant sources, Pharmacological activity.

INTRODUCTION

Natural sources of medicine have gained huge interest as they offer a variety of blessings in a range of activities and eliminate the disadvantages of toxicity and side effects offered by commercial drugs[1]. For indigenous people, plants are the main sources of food and medicine, and our universe is distributed with a rich variety of medicinally important plant species. Black pepper, referred to as the “King of Spices” under the biological name Piper nigrum belonging to the family Piperaceae, is cultivated in tropical regions like Brazil, Indonesia, and India[2]. As a dried fruit, it is a wrinkled drupe about 5mm in diameter. It is an herbal condiment used in cooking as a spice and characterised as a cough suppressant and anti-tussive for immediate relief of colds and coughs[3]. Furthermore, traditional uses include treatment of sore throat, flu, dyspepsia, diarrhoea, muscular pain, carminative, rheumatisim, diuretic, analgesic, antipyretic, anti-toxin, blood purifier, carminative, appetite stimulator, etc.[4]. The

three major chemical constituents in black pepper include 9% piperine, 0.4–7% essential oil, and volatile oils (piperamide and nerolidol)[5]. They offer a wide range of pharmacological activities such as anti-inflammatory, anti-fungal, anti-diabetic, anti-asthmatic, anti-malarial, anti-leukaemia, anti-oxidant, anti-neoplastic, anti-fertility, and immunomodulator. It regulates thermogenic activity by increasing the absorption of vitamins, selenium, and beta-carotene. It is found to increase spatial memory and could be used in the treatment of Alzhemier's disease[6]. The imbalance between the production and accumulation of reactive oxygen species (ROS) in cells and tissues leads to oxidative stress[7]. The underlying factors include lifestyle disorders like obesity, intake of a high-fat diet, cigarette smoking, alcohol consumption, certain medications, pollution, and exposure to pesticides as chemicals[8]. During oxidative stress, there is a generation of free radicals in the body that react with other molecules and cause chain reactions in the body, thereby damaging organs and tissues and resulting in various diseases. The list of diseases due to oxidative stress includes diabetes, atherosclerosis, high blood pressure, heart disease, inflammatory conditions, neurodegenerative diseases like Parkinson's and Alzheimer's, and cancer[9]. Although the cure of these diseases with drugs is a matter of concern and is dependent on various factors such as age, stage of disease, other co-morbidities, and patients' responses, Prevention of one's health from the occurrence of such a diseased condition is widely appreciated, as it provides one with physical and mental well-being. Dietary photochemical such as alkaloids, tannins, saponins, flavonoids, carotenoids, etc. from fruits, vegetables, and spices play an important role in preventive activity as a source of food for daily consumption[10]. This review article discusses in detail about the free radical scavenging capacity of black pepper and its chemical constituents. Most of the lifestyle disorders like diabetes, obesity, cardiovascular disease has oxidative stress linked to be a causative factor. Several formulations of piperine have been evaluated in having efficacy either *In-vitro* or *In-vivo*.

Chemical constituents

Black pepper is a rich source of minerals (potassium (K-0.66%), calcium (Ca-0.20%), phosphorous (P-0.16%), magnesium (Mg-0.16%)) and consists of carbohydrates (37%), proteins (26%) and fats (24%)[11]. The three vital constituents include piperine (9%), essential oil (0.4 to 7%) and volatile oil (1.2 to 5%). Piperine Fig. 1 is the active alkaloid responsible for pungency and bioactivities of pepper ranges from antifungal, antiallergic, anti-ashthmatic, antioxidant, antihypertensive, anti-inflammatory, hepatoprotective and immunomodulatory[12]. It also works as a bioavailability enhancer by inhibiting digestive enzymes thereby improving the therapeutic value of drugs[13]. Piperine exists as four isomeric forms, piperine, isopiperine, chavicine and isochavicine and other alkaloids include piperanine, piperettine, pipercine, piperyline A and piperoline B[14]. The essential oils are responsible for the spicy aroma and characterisitic odor. Monoterepenes (α-pinene, β-pinene, sabinene, 3-carene and camphene), sesquiterpenes (β-caryophyllene), oxygenated monoterpenoids and sesquiterpenoids are components of essential oil[15]. The essential oil shows carminative, larvicidal, stimulant, digestive, tonic,antioxidant, antibacterial and antifungal activities. Piperamides and nerodilol are the volatile oil constituents and shows insecticidal activity[16].

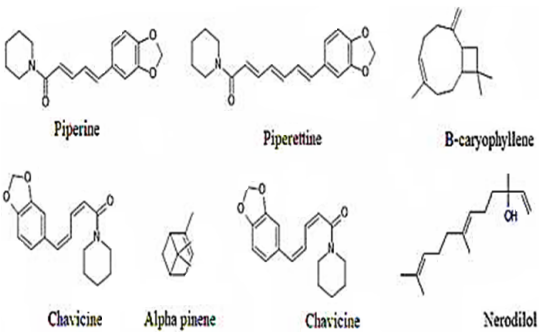

Fig. 1. Chemical constituents of Black Pepper

Pharmacological activities of black pepper

Effects of piperine on increased absorption

Piperine shows inhibitory activity on drug-metabolising enzymes such as cytochrome-P450 and p-glycoprotein in the gastrointestinal mucosa, thereby increasing its oral bioavailability, as reported during clinical trials by the US National Library of Medicine[17]. They are effective inhibitors of first-pass metabolism and increase levels in systemic circulation. Joana Furtado de Figueiredo Neta *et al.,* (2021) conducted a randomised, double-blind, placebo-controlled clinical trial estimating the efficacy of piperine-supplemented *Curcuma longa* L. in metabolically controlling patients with type 2 diabetes mellitus. The study used 71 patients from Brazil, aged

18 years and older, with an administered dose of *Curcuma longa* L. group (500 mg/day with piperine 5 mg) and placebo group for 120 days. It is a known fact that piperine increases curcumin bioavailability by more than 2000%, thereby showing a positive effect for *Curcuma longa* L. The statistical measurements used in this study included fasting venous glycaemia (FVG), glycated haemoglobin (HbA1c), insulin, triglycerides (TGs), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), blood pressure, and body mass index (BMI). It showed a decrease in TG (p.001), FVG, and HbA1c levels.

Oxidative stress and metabolic diseases

Metabolic syndrome (MetS) is a social problem, and the risk factors associated with it are a major public concern. It is an underlying cause for chronic illnesses like excessive body weight, dyslipidemia, hypertension, type 2 diabetes, and atherosclerosis. Oxidative stress is one of the factors for MetS, and the manifestations include obesity, dyslipidemia, and hypertension leading to cardiovascular disease. Chronic inflammation due to higher amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS) causes pathological conditions[18]. Oxidative stress arises due to an imbalance between free radical formation and removal. The toxic free radicals from molecular oxygen include hydrogen peroxide (H_2O_2), superoxide anion (O_2), peroxy radical (ROO-), and reactive hydroxy radical (OH-) that damage the cells of the retina, kidney, heart, and target organs[19]. ROS are by-products of cellular metabolism and act as a second messenger in transducing intracellular signals through various biological processes. They are involved in neurodegenerative disorders, cancer, renal diseases, metabolic diseases, and pulmonary diseases[20].

Antioxidant activity

Exposure to radiation and environmental pollution generates free radicals in the body as a by-product of metabolism. They are causative factors for many diseases, attack the DNA of the cell, and cause mutational changes linked to cancer development. The oxidants have the capacity to attack the cell membrane, leading to lipid oxidation, a reduction in fluidity, and a loss of enzyme and receptor activity, thereby damaging it[21]. Natural antioxidants have gained importance nowadays because of their low cost, wide availability, higher stability, and higher performance[22]. Synthetic antioxidants cause gastrointestinal disorders, allergic effects, and lead to cancer development. A wide variety of plant products claim to be antioxidants, whereas black pepper is an attractive spice that helps in lipid peroxidation and has a natural radical scavenging capacity estimated by human clinical trials. The chemical constituents of pepper, piperine, black pepper essential oil, and oleoresin protect by inhibiting or quenching free radicals and reactive oxygen species[23]. It acts as a cellular antioxidant by lowering lipid peroxidation *In vivo* in conditions of oxidative stress[24].

Cardiovascular effects

Oxidative stress is a triggering factor for various cardiovascular effects. It increases free radical production in the vascular wall, leading to atherosclerosis. Free radicals damage the DNA, thereby promoting apoptosis and cell senescence. The increase in the plasma cholesterol level, especially the low-density lipoprotein cholesterol (LDL-c) in the arterial wall, and the modification of ROS by enzymes such as NADPH oxidase, superoxide dismutase, xanthine oxidase, and nitric oxide synthase enhance the degree of oxidation and increase the severity of the disease[25]. The cascade of vascular changes results in the narrowing of cells, leading to angina pectoris, coronary artery disease, and myocardial infarction.

Myocardial ischemia

Myocardial infarction is a condition in which there is an ischemic death of the tissues of the myocardium. It may be due to thrombotic occlusion of the coronary vessel that is ruptured by the formation of plaque. The deposition of cholesterol, fats, cellular waste products, and fibrin in the subepicardium causes mitochondrial alterations that are permanently involved in the apoptosis of cardiomyocytes in the infarcted heart[26]. The increased serum levels of creatine kinase (CK) and lactate dehydrogenase (LDH) are diagnostic markers of a diseased heart. Piperine has shown antioxidative and dyslipemedic effects in reducing CK and LDH levels.[26] It reduces the ROS, protein carbonyl content, glutathione-S-transferase (GST), and catalase in heart tissues, causing a reduction of free radicals that damage the myocardial cells.

Atherosclerosis

Plaque deposition on the inner lining of the

arterial wall narrows and hardens the arteries. There is excessive accumulation of plasma LDL and TC in atherosclerosis. Hyperlipidemia is the pathological condition characterising the disease condition atherosclerosis[27]. It is a chronic inflammation in the walls of the endothelium and is influenced by various adhesion molecules by suppressing transporters like NFB activation[28]. Piperine shows a protective factor by inhibiting lipid peroxidation and acting as an oxide and hydroxy radical scavenger, reducing lipid peroxidation and TG accumulation. It also reduced plasma TC, VLDL, LDL-c, and the activity of HMG-CoA. It enhances the excretion of bile acids and natural sterols[29].

Anti-hypertensive effect

High blood pressure is a risk factor for cardiovascular diseases. It increases the workload on the heart, causing structural and functional changes in the myocardium. It is associated with diseases like coronary artery disease, cerebral stroke, renal failure, ventricular hypertrophy, etc. It causes hypertrophy of the left ventricle, causing heart failure, arrhythmias, atrial fibrillation, and an increased risk of coronary artery disease[30]. Piperine shows blood pressure-lowering and vasomodulatory effects by blocking voltage-dependent Ca^{2+} channels that are responsible for cardiodepressant and vasodilator activities, providing a pharmacological basis for antihypertensive activity[31]. Other mechanisms include decreased ROS generation, uric acid concentrations, C-reactive protein (CRP), and the antioxidative activity of piperine[32].

Anti-inflammatory activity

Inflammation is a process in which the immune system is compromised and subjected to cellular responses activated by NF-B proinflammatory mediators. Activating NF-B activates proinflammatory genes such as cytokines (interleukins and tumour necrosis factor), adhesion molecules, and enzymes like Cyclooxygenase 2, and induces nitric oxide synthase (iNOS)[33]. Oxidative stress produces excess reactive oxygen species (ROS) and activates genes in inflammatory pathways that damage cellular molecules[34]. Nayara Cristina Freitas e Silva-Santana *et al.,* (2022 studied the effect of turmeric supplementation with piperine in a randomised, double-blinded clinical trial conducted on haemophilia patients of the age group 20–75 years. Piperine acts as a bioavailability enhancer of turmeric and is found to show superior antioxidant activity in comparison to turmeric[34].

Anti-Diabetic activity

Oxidative stress and free radical generation lead to hypoglycemia and the pathogenesis of diseases like diabetes and cardiovascular disease[35]. Antioxidants have a scavenging capacity, but when the limit exceeds the defence systems, it leads to apoptosis, cell dysfunction, and cell death. Oxidative stress leads to the loss of pancreatic cells, cell injury and dysfunction, and cell death that led to the onset of diabetes. Chronic hyperglycemia is associated with risk factors for cardiovascular diseases and the progression of cancer cells[36]. The fruits and leaves of black pepper are found to show *In vitro* alpha-glucosidase, alpha-amylase, and aldose reductase inhibitory activity, increased glucose consumption by adipocytes, induced transactivation of PPARA, and in vivo alloxan/streptozotocin-induced diabetic rats with reduced hyperglycemia, reduced hyperlipedemia, increased serum insulin levels, improved antioxidant status, and improved liver function[37]. Black pepper extract improves insulin levels, signifying its usage in the management of hyperglycemia[38]. Thanutchaporn Nutmakul *et al.,* (2023) studied the synergistic effect of Trikatuk, a traditional Thai formulation, for its anti-oxidant and alpha glucosidase inhibitory effects. Alpha glucosidase enzymes are responsible for hydrolyzing carbohydrates into glucose, and their inhibition delays the absorption of glucose, reduces postprandial hyperglycemia, and retards the liberation of glucose from carbohydrate. Trikatuk is a Thai formulation comprised of three fruits of *Piper nigrum* L. and *Piper retrofractum Vahl* and the *rhizomes* of *Zingiber officinale Rosco*[39,40]. This study revealed the efficiency of *Piper nigrum* L and *Piper retrofractum* in contributing to alpha-glucosidase inhibitory activity due to their high piperine content. ViphyllinTM is a standardised black pepper extract proprietary to Vidhya Herbs Pvt.Ltd. Bangalore, India, prepared from that contains not less than 30% of -caryophyllene (BCP) that exerts oral hypoglycaemic activity. Studies were conducted on diabetic rats, and it was found to exert antidiabetic effects and improve nerve conduction to mitigate neuropathic pain[41]. It is a cannabinoid receptor 2 (CB2) agonist with potential pharmacological actions such as dyslipedemia and hyperglycemia.

Anti-Cancer activity

Cancer is the uncontrolled growth and division of cells due to biochemical and genetic alterations. Although treatment is difficult, prevention would be a prophylactic strategy for reducing the global burden of cancer. It is reported that about 30–40% of cancers can be prevented through dietary modifications and preventing exposure to environmental carcinogens[42]. Piperine, the most active alkaloid of black pepper, is a dietary photochemical with chemopreventive potential. It has activity on many different types of cancers, such as breast cancer, ovarian cancer, lung cancer, gastric cancer, prostate cancer, cervical cancer, leukaemia, etc., and has an influence on the activation of apoptotic signalling and inhibition of cell cycle progression[43]. It exhibits anti-cancer activity by altering redox homeostasis, causing cell cycle arrest, inhibiting self-renewal of cancer stem cells, influencing autophagy in favour of cell death, inhibiting angiogenesis, influencing the activity of drug metabolising enzymes, inhibiting p-glycoprotein activity, and enhancing the bioavailability of drugs[44,45]. Piperine is a potent inhibitor of p-glycoprotein [P-gp] and MRP and has a significant effect on drug metabolising enzymes. Table 1 represents the role of pepper and its mechanism of action. Table 1. Pharmacological activity of Black pepper and its mechanism of action.

Table 1: Pharmacological activity of Black pepper and its mechanism of action

S. No	Pharmacological Activity	Mechanism of Action
1	Antioxidant	Prevents lipid oxidation and acts as a natural radical scavenger
2	Myocardial Ischemia	Shows Dyslipidaemia effect by reducing the levels of Creatine Kinase (CK) and Lactate Dehydrogenase (LDH)
3	Atherosclerosis	Inhibits lipid peroxidation and acts as an oxide and hydroxy Radical scavenger, reduces plasma LDL, VLDL, TC and activity of HMG-CoA
4	Anti-hypertensive	Blocks Voltage sensitive Ca^{2+} dependent channels and acts as a cardio depressant and vasodilator activity
5	Anti-inflammatory	Inhibitor of NF-B and COX-2 inflammatory pathways
6	Anti-diabetic	Inhibitor of Alpha glucosidase and reduces post-prandial hyperglycaemia
7	Anti-cancer	Inhibitor of drug metabolising enzymes like p-glycoprotein [P-gp] and enhances bioavailability of drugs

CONCLUSION

Pepper is one of the oldest and most extensively used spices and traditional medicines by mankind. As a spice in the kitchen, it is used as a daily source of food in the diet. Apart from the culinary uses, the pharmacological applications of black pepper in *In vitro* and human clinical trials necessitated the need to identify the relationship between oxidative stress and its efficacy as a natural free radical scavenger. The cellular damage caused by oxidative stress is the underlying causative factor for many chronic diseases like inflammation, cardiovascular diseases, diabetes, and cancer. This review article discusses pepper and its alkaloid piperine, which shows *In vitro* animal activity for anti-oxidant, anti-inflammatory, cardio vascular disease, anti-diabetic, and anti-cancer activities.

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Conflict of interest

We declare that there is no conflict of interest.

REFERENCES

1. Briskin, D. P.; *Plant physiology.,* **2000**, *124*(2), 507–14.
2. Saleem A.; Naureen I.; Naeem M.; Tasleem G.; Ahmed H; Farooq U.; *Sch Int J Biochem.,* **2022**, *5*(1), 15–21.
3. Morice A.H.; McGarvey L.; Pavord I.; *Thorax.*, **2006**, *61*(suppl 1), i1-24.
4. Ashokkumar, K.; Murugan, M.; Dhanya, M.K.; Pandian, A.; Warkentin, T.D.; *Clinical Phytoscience.*, **2021**, *7*(1), 1-1.
5. Lee J.G.; Chae, Y.; Shin, Y.; Kim, Y.J.; *Applied Biological Chemistry* ., **2020**, *63*(1), 1-9.

6. Subedee, L.; Suresh, R. N.; Jayanthi, M. K.; Kalabharathi, H. L.; Satish, A. M.; Pushpa, V. H.; *J. Clin. Diagnostic Res.*, **2015**, *9*(4), FF01.
7. Sharifi-Rad, M.; Anil Kumar, N.V.; Zucca, P.; Varoni, E.M.; Dini, L.; Panzarini, E.; Rajkovic, J.; Tsouh Fokou, P.V.; Azzini, E.; Peluso, I.; Prakash Mishra, A., *Frontiers in physiology.,* **2020**, *11*, 694.
8. Carraro, E; Schilir, T; Biorci, F; Romanazzi, V; Degan, R; Buonocore, D; Verri, M; Dossena, M; Bonetta, S; and Gilli, G; *Int. J. Environ. Res. Public Health.*, **2018**, *15*(6), 1152.
9. Pizzino, G.; Irrera, N.; Cucinotta, M.; Pallio, G.; Mannino, F.; Arcoraci, V.; Squadrito, F.; Altavilla, D.; Bitto, A.; *Oxid. Med. Cell. Longev.,* **2017**, 8416763.
10. Probst YC.; Guan VX and Kent K.; *BMJ open.*, **2017**, *1,7*(2), e013337.
11. Pradeep KU.; Geervani P.; and Eggum BO.; *Plant Foods Hum Nutr.*, **1993,** *44*, 137-48.
12. Qu H.; Lv M.; Xu H.; *Mini Rev Med Chem.,* **2015**, *15*(2), 145-56.
13. Johnson JJ.; Nihal M.; Siddiqui IA.; Scarlett CO.; Bailey HH.; Mukhtar H.; Ahmad N.; *Mol Nutr Food Res.*, **2011**, *55*(8), 1169-76.
14. Milenkovi A.N.; Stanojevi L.P.; *Advanced Technologies.*, **2021**, *10*(2), 40-50.
15. Kumoro A.C.; Hasan M.; and Singh H.; *Arab. J. Sci. Eng.*, **2010**, *35*, 7-16.
16. Ashokkumar K.; Murugan M.; Dhanya MK.; Pandian A.; Warkentin T.D.; *Clinical Phytoscience.*, **2021**, *7*(1), 1-1.
17. Luo H.; Li Z.; Straight C.R.; Wang Q.; Zhou J.; Sun Y.; Lo C.Y.; Yi L.; Wu Y.; Huang J.; Wolfe W.; *Food Chem.*, **2022**, *373*, 131277.
18. Rezzani R.; Franco C.; *Nutrients.*, **2021**, *13*(2), 301.
19. Kang Q.; Yang C.; *Redox Biol.,* **2020**, *37*, 101799.
20. Incalza M.A.; D'Oria R.; Natalicchio A.; Perrini S.; Laviola L.; and Giorgino F. ; Vascul. *Pharmacology.*, **2018**, *100*, 1-9.
21. Vijayakumar R.S.; Surya D.; Nalini N.; *Redox Report.*, **2004**, *9*(2), 105-10.
22. Xiu-Qin L.; Chao J.; Yan-Yan S.; Min-Li Y.; Xiao-Gang C.; *Food Chem.*, **2009**, *113*(2), 692-700.
23. Jiang TA.; *J. AOAC Int.,* **2019**, *102*(2), 395-411.
24. Kaleem M.; Sheema S.H.; Bano B.; *Indian J Physiol Pharmacol.*, **2005**, *49*(1),65-71.
25. Lorenzon dos Santos J.; Schaan de Quadros A.; Weschenfelder C.; Bueno Garofallo S.; Marcadenti A.; *Nutrients.*, **2020**, *12*(3), 682.
26. Frangogiannis N.G.; *Compr. Physiol.,* **2011**, *5*(4), 1841-75.
27. Wang D.; Atanasov A.G.; *Int. J. Mol. Sci.,* **2019**, *20*(2), 324.
28. Kumar S.; Singhal V.; Roshan R.; Sharma A.; Rembhotkar G.W.; Ghosh B.; *Eur. J. Pharmacol.*, **2007**, *575*(1-3), 177-86.
29. Wang D.; Uhrin P.; Mocan A.; Waltenberger B.; Breuss J.M.; Tewari D.; Mihaly-Bison J.; Huminiecki.; Starzyski R.R.; Tzvetkov N.T.; Horbaczuk J.; *Biotechnol. Adv.*, **2018**, *36*(6), 1586-607.
30. Diamond, J.A.; and Phillips, R.A.; *Hypertens. Research.*, **2005**, *28*(3), 191-202.
31. Taqvi S.I.; Shah A.J.; Gilani A.H.; *J. Cardiovasc. Pharmacol.*, **2008**, *52*(5), 452–8.
32. Diwan V.; Poudyal H.; Brown L.; *Cell Biochem. Biophys.*, **2013**, *67*, 297–304.
33. Pei H.; Xue L. Tang M.; Tang H.; Kuang S.; Wang L.; Ma X.; Cai X.; Li Y.; Zhao M.; Peng A.; *J. Agric. Food Chem.*, **2020**, *68*(8), 2406–17.
34. Silva-Santana N.C.; Rodrigues H.C.; Martins T.F.; Braga C.C.; Silva M.A.; da Cunha L.C.; de Souza Freitas A.T.; Costa N.A.; Peixoto M.D.; *Free Radic. Biol. Med.*, **2022**, *193*, 648–55.
35. Nutmakul T.; Chewchinda S.; *Heliyon.*, **2023**, e13063.
36. Giri B.; Dey S.; Das T.; Sarkar M.; Banerjee J.; Dash S.K.; *Biomed. Pharmacor.,* **2018**, *107*, 306-28.
37. Pereira A.S.; Banegas-Luna A. J.; Pea-Garca J.; Pérez-Sánchez H.; Apostolides Z.; *Molecules.*, **2019**, *24*(22), 4030.
38. Sarfraz M.; Khaliq T.; Hafizur R.M.; Raza S.A.; Ullah H.; *Endocrine and Metabolic Science.*, **2021**, *4*, 100098.
39. Lim T.K.; *Fruits.*, **2012**, 351–7.
40. Tappayuthpijarn P.; Sattaponpan C.; Sakpakdeecharoen I.; Ittharat A.; *Thai J. East Asian Stud.*, **2012**, *17*(1), 18–25.
41. Ramanaiah I.; Sudeep HV.; and Shyamprasad K.; ViphyllinTM.; *Diabetes Metab. Syndr. Obes.: Targets Ther.*, **2022**, 1819–29.
42. Donaldson M.S.; *Nutr. J.*, **2004**, *3*(1), 1-21.
43. Mitra S.; Anand U.; Jha N.K.; Shekhawat M.S.; Saha S.C; Nongdam P.; Rengasamy K.R.; Proków J.; Dey A.; *Front. Pharmacol.*, **2022**, *12*, 772418.
44 Lal M.; Gangotri K. M; *Int. J. Energy Res.,* **2022**, *46*(14), 19538-19547.
45. Rakesh Kumar A.; Sharma P.; Lal M. *Indian J Sci Technol.*, **2022**, *15*(23), 1159-1165.