International Research Journal of Biological Sciences ISSN 2278-3202
Vol. **13(3),** 27-32, August **(2024)** *Int. Res. J. Biological Sci.*

Review Paper

Nature's Pharmacy: Avocado (*Persea americana* Mill.) Leaves as a Novel Therapeutic Agent for Diabetes, Hypertension, High Cholesterol, Gastric Ulcers, Kidney Stones and Gout

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Available online at : www.isca.in, www.isca.me
Received 1st May 2024, revised 18th May 2024, accepted 29th May 2024

Abstract

Non-communicable diseases originating from a combination of genetic, physiological, environmental and behavioural factors are threatening livelihoods of mankind. They kill approximately 41 million people each year, equivalent to 74% of all deaths globally. Avocado leaves harbour bioactive substances that could help managing a range of non-communicable diseases. The aim of this article is to review the therapeutic potential of such leaves in managing diabetes, hypertension, high cholestero1, kidney stones, gastric ulcers and gout. Avocado leaf extracts at a dosage of 100 mg/kg/day effectively reduced blood glucose levels in diabetic rats and thus managed type 2 diabetes throughout a four-week treatment period. The extracts managed hypertension by lowering systolic blood pressure from 164.9 ± 7.2 to 116.8 ± 6.4 mmHg and diastolic blood pressure from 118.4 ± 16.2 to 82.8 ± 6.5 mmHg. The extracts regulated plasma cholesterol levels by increasing high-density lipoprotein cholesterol (good cholesterol) and lowering total cholesterol, triglycerides and high-density lipoprotein cholesterol (bad cholesterol). Additionally, the extracts prevented oxidant damage and crystal formation and deposits in the white rat kidneys. The extract managed gastric ulcers by reducing gastric acid secretion and ulcer count/index. As for the management of gout, avocado leaf extract demonstrated ability of lowering blood uric acid content (from 12.3 to 4.3%) whose higher levels result into gout. This suggests that avocado leaf could be processed into conventional drugs for managing such non communicable diseases.

Keywords: Bad cholesterol, blood pressure, chronic diseases, hypoglycaemic activity, natural products, and uric acid.

Introduction

Non-communicable diseases refer to chronic medical conditions or diseases that are non-infectious or non-transmissible[1]. They result from a combination of genetic, physiological, environmental and behavioural factors. Approximately 41 million people die from non-communicable diseases each year, equivalent to 74% of all deaths globally. Tobacco use, physical inactivity, excessive alcoholism, unhealthy diets and air pollution increase the risk of dying from non-communicable diseases[2]. Non-communicable diseases include diabetes, gastric ulcers, hypertension, high cholesterol, kidney stones and gout.

Diabetes occurs due to inability of the pancreas to produce enough insulin or inability of the body to effectively utilize the insulin it produces. Insulin is a hormone responsible for regulating the amount of blood glucose[3]. Uncontrolled diabetes may result into hyperglycaemia or raised blood sugar, which over time could result into damages to many body organs, including the nerves and blood vessels. The number of diabetic people increased from 108 million (1980) to 422 million (2014). The prevalence of diabetes is rising more rapidly in low- and middle-income countries than in high-income countries. From 2000 and 2019, there was a 3% increase in diabetes mortality rates by age globally, whereas in 2019, about 2 million deaths resulted from diabetes and its associated kidney disease[3].

Hypertension, also known as high or raised blood pressure (systolic blood pressure/diastolic blood pressure of ≥ 140/90 mmHg), is a global public health issue disproportionately affects populations in low- and middle-income countries where health systems are weak[4]. This common, deadly condition leads to stroke, heart attack and failure, kidney damage and many other health complications. Hypertension affects approximately 1.28 billion adults aged 30-79 worldwide, with the majority of cases (two-thirds) occurring in low- and middle-income nations. Statistics indicates that about 60% of the population develop hypertension by 60 years of age and approximately 65 and 75% of men and women, respectively, develop hypertension by 70 years[5]. Alarmingly, 46% of persons with hypertension are unfamiliar with their disease, while only 42% get diagnosed and treated. Even more troubling is the fact that only 21% (1 in 5 adult patients) have their hypertension under control[4].

Cholesterol is a waxy substance produced by animal liver and also supplied in diet through animal products such as meats, poultry, fish and dairy products[6].

The body needs cholesterol for insulating nerves, making cell membranes and producing certain hormones. Nevertheless, the body produces sufficient cholesterol in such a way that it does not need any dietary cholesterol[7]. Cholesterol can be categorized into good and bad cholesterol, for instance high-density lipoprotein (HDL) is good cholesterol whereas low-density lipoprotein (LDL) is bad cholesterol[7]. Elevated cholesterol levels in serum is a leading risk factor for human cardiovascular diseases including atherosclerosis, coronary heart disease, stroke and heart attack[8]. Excess cholesterol in the bloodstream builds up thick, hard deposits in artery walls causing arteries to be thicker, harder and less flexible thereby slowing down and sometimes blocking blood flow to the heart which may lead to chest pain and heart attack. High total cholesterol is a major cause of disease burden in both the developed and developing world as a risk factor for ischemic heart disease and stroke[7]. About 39% of adults worldwide are affected by elevated total cholesterol and approximately 4.4 million deaths (7.8% of all deaths) occurred in 2019 were caused by elevated bad cholesterol[9].

Gastric ulcers are >5 mm diameter breaches in the mucosal barrier of the stomach lining that infiltrate through the muscularis mucosa[10]. The disease is mostly caused by Helicobacter pylori infection and gastric prostaglandin loss caused by non-steroidal anti-inflammatory medications. Other causes include viral infections such as Cytomegalovirus, hypergastrinemia, chemotherapy and radiation, gastric outlet obstruction, gastric infiltrative disorders such as malignancy, and cigarette smoking. The unifying denominator among all of these aetiologies is that they cause a breach in the mucosal barrier, exposing the gastric mucosa to acid's harmful effects[10,11].

Kidney stone disease, also known as urolithiasis or nephrolithiasis, is urological disease involving precipitation of urinary solutes into aggregates of crystalline material in the urinary tract[12]. Kidney stones could be uric acid, calcium phosphate, calcium oxalate, struvite, and mixed stones, of which calcium stones are the most common accounting for 70 to 80% of the stones[13]. The disease affects about 15% of the world population across all ages and sexes although it occurs more frequently in males than in females within 20–49 age[14]. Epidemiological studies have linked kidney stone disease with hypertension, cardiovascular disease, diabetes, obesity, metabolic syndrome, among others[15].

Gout is a common form of inflammatory arthritis which is very painful that if not treated can last for weeks leading to intense pain, work absence, erectile dysfunction, cardiovascular events, and hospitalisations[16-19]. It is caused by hyperuricemia, i.e.: an elevated serum uric acid level of > 6 mg/dL in women and > 7 mg/dL in men. The elevated serum uric acid causes building up of uric acid crystals in joints, fluids, and tissues within the body[20]. The gout prevalence across the globe per 100,000 population increased from 145 (in 1990) to 176 [21].

Proper and effective management of the non-communicable diseases is becoming progressively important in order to lower long-term complications of such diseases and enhance the quality of life of the victims[22,23]. Research on the use of natural ingredients to manage such diseases is drawing more attention in an effort to develop alternative therapies that may be beneficial to health in addition to conventional medication[24].

Avocado (*Persea americana* Mill.) leaves are one of natural ingredients that have traditionally been used by many cultures across the globe as anti-diabetic and anti-hypertension, *inter alia*[25]. The leaves, often overshadowed by avocado fruit, carry a treasure trove of bioactive compounds including polyphenols, flavonoids, carotenoids and essential oils that contribute to a wide range of therapeutic effects[26]. The present article reviews the therapeutic potential of avocado leaves in managing diabetes, hypertension, high cholesterol, kidney stones, gastric ulcers and gout.

Antidiabetic potential of avocado leaves

The avocado leaf possesses potent antioxidant and α-amylase inhibition abilities that may control blood glucose levels in managing type 2 diabetes. The leaf contains a number of flavonoids and phenolic acids responsible for this property[27]. Lima et al.[28] investigated the hypoglycaemic action of the avocado leaves hydro-alcoholic extract, and its molecular mechanism in lowering the blood glucose levels via the protein kinase B signalling pathway in diabetes induced by streptozotocin in rat. They discovered that the avocado leaf hydroalcoholic extract was hypoglycaemic and improved the animals' metabolism. It was noted that protein kinase B found in the liver and the muscles of rats was activated by the avocado leaf extract, indicating some possible molecular mechanisms of its action on diabetes.

Similarly, Antia et al.[29] explored the hypoglycaemic activity of the aqueous leaf extract of avocado plant. They found that giving 100 to 200 mg/kg body weight (BW) of the extract to alloxan-induced diabetic rats caused a significant and dose-related decline in blood glucose levels both after a single dose and following a 7-day treatment. In addition to that they noticed that the maximum antidiabetic effect occurred at 6 hours after a single dose with a 60.02 ± 6.83% reduction in blood glucose levels. However, the extract's hypoglycaemic activity was not comparable to that of the reference drug (chlorpropamide). Throughout the 7-day treatment period, the extract (100–200 mg/kg) consistently exhibited significant antidiabetic activity, maintaining a sustained reduction in blood glucose levels compared to the control group.

Additionally, Kouamé et al.[30] discovered that extracts from avocado leaves exhibited significant antidiabetic effects in type 2 diabetic rats. The aqueous, ethanolic and methanolic extracts of avocado leaves at a dosage of 100 mg/kg/day successfully decreased blood glucose levels in diabetic rats, effectively managing type 2 diabetes throughout a 28-day treatment period.

Anti-hypertensive properties of avocado leaves

Ojewole et al.[31] determined the cardiovascular impact of avocado leaf extracts on animals. The extracts displayed a concentration dependent negative effect on atrial muscle of the guinea pigs as well as an antagonistic activity with regard to noradrenaline and calcium induced positive inotropy and chronotropism of isolated atrial muscle strip. Furthermore, the extracts decreased contractions of portal veins in experiments with Wister rats while inducing vasorelaxation of in aortic rings. Vasorelaxation effects of the extracts on rats with normal blood pressure and high blood pressure led to dose-related decrease in blood pressures and heart rates. The avocado leaf extracts-mediated bradycardia, vasorelaxation, and hypotension indicates the potential of avocado leaf extract as a natural remedy on essential hypertension and selected cardiac disorders. These findings are consistent with those of Sutiningsih et al.[32] who found that avocado leaf extract and its nanoparticles were efficient in treating salt-induced hypertension. The leaf extract reduced systolic and diastolic blood pressures from 164.9 ± 7.2 to 116.8 ± 6.4 mmHg and 118.4 ± 16.2 to 82.8 ± 6.5 mmHg, respectively, while nanoparticles proved superior, dropping systolic and diastolic blood pressures from 175.0 ± 21.6 to 106.3 ± 9.2 mmHg and 128.4 ± 25.8 to 73.2 ± 15.8 mmHg, respectively[32]. Given the global prevalence of hypertension diseases among people of all genders and ages, the findings imply that avocado leaf might be made into a useful drug for treating high blood pressure among hypertensive patients.

Avocado leaves in managing elevated cholesterol levels:

Research suggests that avocado leaves may contribute to cholesterol regulation by reducing LDL cholesterol levels and promoting HDL cholesterol. Brai et al.[25] investigated the impact of aqueous and methanolic leaf extracts from avocado on total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) in rats. They induced hypercholesterolemia through feeding the rats with a diet high in groundnut oil, cholesterol and cholic acid. Rats were then treated daily with either aqueous or methanolic extracts of avocado leaf (10 mg/kg of body weight) for 8 weeks. The researchers discovered that treatment with aqueous and methanolic avocado leaf extracts induced reductions in TC (8% and 5%, respectively), and LDL-C (19% and 20%, respectively). Additionally, plasma HDL-C concentrations increased by 85% and 68%, respectively, in the aqueous and methanolic extract-treated rats compared to hypercholesterolemic controls. This suggest that avocado leaf extracts may influence lipid metabolism and potentially provide protective effects against atherosclerosis development in hypercholesterolemic rats.

Likewise, Brai et al.[33] investigated the potential effects of pre-treating Wistar male albino rats with the aqueous extract of avocadoleaves (AEAL) on total cholesterol (TC), triacylglycerols (TAG), and hematological parameters in the presence of CCl_4-induced intoxication.

The study included a healthy control group (Group 1), a standard drug pre-treatment group with Reducdyn® (Group 2), and AEAL pre-treatment groups at doses of 100 mg/kg (Group 4) and 200 mg/kg (Group 5). Treatments were orally administered for seven days, followed by CCl_4 injection on the seventh day. They found that pre-treatment with AEPA significantly reduced TC (19–34%) compared to CCl_4 alone. Furthermore, the study noticed a significant decrease in serum TAG concentration with AEAL pre-treatment. These findings suggest that AEAL may offer protection against fatty liver development.

Similarly, Kolawole et al.[34] investigated the effects of methanolic avocado leaf extract on rats that had been induced to develop hyperlipidemia due to cholesterol. The rats were split into five groups: three treatment groups received the cholesterol diet plus the leaf extract at doses of 20 and 40 mg/kg body weight, or cholestyramine; a normal control group received distilled water; and a cholesterol-induced hyperlipidemic control group received a cholesterol-rich diet. In hyperlipidemic rats, administration of the extract over an eight-week period rectified, in a dose-dependent manner, alterations in plasma levels of triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC). They noticed that the leaf extract significantly increased HDL levels by 60.0% at 20 mg/kg BW, while drastically lowering TC, TG and LDL-C levels by 54.2%, 46.2% and 65.6%, respectively. Furthermore, the extract decreased LDL-C, TG, and TC levels by 87.5, 69.2, and 60.4%, respectively at a higher dosage of 40 mg/kg, while it increased HDL-C levels by 80.0%. Additionally, the extract lowered the rats' plasma lipid peroxidation in a dose-dependent manner with the extract's antihyperlipidemic activity being equivalent to that of cholestyramine, the standard medication.

Similar findings were obtained by Kouamé et al.[30] who observed that avocado leaf extract regulated the lipid profile of diabetic rats, restoring TC and HDL-C levels to normal while reducing TG levels, very low-density lipoprotein cholesterol (VLDL-C), and total lipoprotein (T-LIP) as well as LDL-C and the atherogenic index of plasma (AIP). These results imply that avocado leaf may be a viable substitute therapy for hyperlipidemia, although more investigation is required to clarify its mode of action.

Avocado leaves in managing kidney Stones

Avocado leaves may aid in preventing kidney stone formation. Erdem et al.[35] assessed the effects of avocado leaves on nephrolithiasis using an animal model with 42 rats. The groups received both 0.5 and 1 ml doses of avocado leaves ethanolic extracts orally for 28 days. They noticed that avocado extracts increased urine volume and urine citrate levels, while decreasing urine cystine and oxalate levels. Moreover, the extracts reduced crystal deposits in kidney tissue and prevented oxidant damage and crystal formation.

Likewise, Wientarsih et al.[36] investigated the anti-lithiasis activity of avocado leaf extract in a nephrolithiasis model induced by ethylene glycol and ammonium chloride in white male rats. Twenty adult male white rats were divided into four groups with different induction treatments, including aquadest, 0.75% ethylene glycol and 2% ammonium chloride, and avocado leaf extract at levels of 100 and 300 mg/kg body weight respectively. At the conclusion of the trial, the calcium level and inhibitory activity against the formation of calcium oxalate crystals in the kidneys were analysed. The results indicated a significant decrease in the calcium oxalate crystals level in the kidneys of rats treated with avocado leaf extract compared to those treated with 0.75 % ethylene glycol and 2% ammonium chloride. The avocado leaf extract demonstrated potential as an herbal remedy, particularly for preventive measures against urolithiasis diseases.

Similarly, Sandhiutami et al.[37] investigated the impact of avocado leaf infusion on the dissolution of urinary stones in white male rats. They divided twenty-four male white rats into the negative control group (received no infusion) and groups receiving orally avocado leaf infusion at doses of 1, 2 and 3 g/kg BW for seven consecutive days following the placement of black silk thread as the stone core in the urinary tract. They noticed significant differences among the treatment groups in terms of urinary stone weight and volume, with the 3g/kg BW group showing the most effective dissolution of bladder stones.

Anti-ulcer potential of avocado leaves

Owoyele et al.[38] investigated the effectiveness of avocado leaf aqueous extract in remedying indomethacin and ethanol/HCl-induced ulcers in rats along with its impact on gastric acid secretion. They found that oral administration of rats with 100 and 200 mg/kg BW of the extract significantly reduced ulcer index from 4.0 ± 0.2 to 0.1 ± 0.1 (in indomethacin-induced ulceration) and from 4.5 ± 0.2 to 0.5 ± 0.1 (in ethanol/HCl-induced ulceration) and at the same time decreased the secretion of gastric acid. Similar findings were obtained by Simbolon et al.[39] who revealed that administering 400 mg/kg BW of avocado leaf ethanolic extract for eight-day duration to rats with aspirin-induced gastritis produced anti-inflammatory effects that were comparable to that of a standard drug Cimetidine. These effects included reduction in gastric fluid concentration, ulcer count and index along with an increase in gastric pH. These findings suggest that avocado leaves possess anti-ulcer properties that could be harnessed into development of standard drug for mitigating gastritis and gastric ulcers.

Avocado leaves in gout management

Amis et al.[40] evaluated antihyperuricemia activity of avocado leaf ethanolic extract in rat induced with potassium oxonate. They found that the extract had significantly xanthine oxidase (the main biochemical index for hyperuricemia and gout) inhibitory activity in the in vitro analysis, having a percentage inhibition of 91.71 % at 120 ppm. The in vivo assays on the rats induced with potassium oxonate showed impressive findings regarding the ethanolic extract in dosage amount of 300 mg/kg that led to the reduction in uric acid content in blood from 12.3 to 4.3 %, which was comparable to the 3.5 % caused by the allopurinol, the standard medication. This indicates that avocado leaf extract could be used in a natural way as a future biomedical anti-hyperuricemia agent.

Conclusion

Avocado leaves have potential of managing non-communicable diseases including diabetes, hypertension, high cholesterol, kidney stones, gastric ulcers and gout. To fully utilize these properties, more rigorous clinical studies are warranted to establish their mechanism of action, optimal dosage, drug formulations and modes of delivery as well as potential side effects of the formulated drugs.

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