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R E V I E W   A R T I C L E

Drug utilization studies in metabolic disorder

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A B S T R A C T

Hibiscus cannabinus (Kenaf) is a potential source of bioactive constituents and natural antioxidant. The current study determined the impact of various solvents on extraction yield, recovery of polyphenol and flavonoid, antioxidant, anticancer, and antibacterial properties of Kenaf leaves and seed. The powder of leaves and seed was separately extracted with *n*-hexane, ethyl acetate, ethanol, and water solvent. Among them, the ethanol extract of leaves and seed showed the highest extraction yield, and their GC-MS analysis revealed a total of 55 and 14 bioactive compounds, respectively. The total polyphenols (TP) and flavonoids (TF) content were quantified by a spectrophotometric technique where water extracts displayed a noteworthy amount of TP and TF content compared to other extracts. A similar demonstration was noticed in antioxidant activity, evaluated by DPPH (2,2-diphenyl-1-picrylhydrazyl) and hydrogen peroxide scavenging capacity. In addition, cytotoxicity and anti-lung cancer activity were identified against mouse embryonic fibroblast (NIH3T3) and human lung cancer (A549) cells.

Keywords: *Hibiscus cannabinus*, polyphenol, flavonoid, anti-lung cancer activity

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C O N T E N T S

1. Hypertension

Hypertension is a chronic metabolic disorder with persistent elevation of Blood Pressure (BP) in the arteries (1) BP is Commonly expressed as the ratio of the systolic BP and diastolic BP (Normal BP was 120-129/80-85mmHg) (2). According to JNC (Joint National Committee) Hypertension is classified into 3 types based on Blood Pressure: High normal Hypertension (130-139/85-89mmHg), Grade-1 Hypertension (140-159/90-99mmHg), Grade-2 Hypertension (>160- 170/100-109mmHg) (31. It often also called the "silent killer" because it often has no warning signs or symptoms, and many people do not realize they have it 14). Hypertension escalates the probability of developing atherosclerosis, myocardial infarction, heart failure, renal failure, cerebrovascular accident, aneurysm, and retinal hemorrhage and visual impairment (s-A wide-

reaching predominance of hypertension surpasse 1.13 billion people worldwide (3]. In 2015 1 in 4men and 1 in 5 women had hypertension and fewer than 1 in 5 people with hypertension have problem under control. Hypertension is a major cause of premature death worldwide. It is a major public health problem due to its high prevalence all around the Globe. According to NFHS-5 prevalence of Hypertension among age 15 years and above (BP >140/90mmHg) in women and men are 25.3% and 29.0% respectively in urban and rural (2019-2020).

According to the International Diabetes Federation (IDF), for a patient to be diagnosed with metabolic syndrome, the person must have central obesity (defined by waist circumference with ethnicity specific values) plus any two of the following conditions: raised TG, reduced HDL cholesterol, raised blood pressure, and increased fasting plasma glucose (3). Metabolic syndrome has emerged in recent years as a major public health concern due to its increasing global prevalence. This disorder has profound implications as afflicted individuals have been demonstrated to be at increased risk of development of hypertension, atherosclerosis, type 2 diabetes and cardiovascular disease

2. Diabetes

Diabetes is a chronic metabolic disorder that occurs either when the pancreas does not produce enougi insulin or when the body cannot effectively use the insulin it produced. There are mainly two types of diabetes: Type-1 diabetes is immune- mediated and requires daily administration of insulin. The common type is Type-2 diabetes and characterized by insulin resistance or relative insulin deficiency 9, 10}- Type 2 diabetes is the most common form and comprises of 90% of people with diabetes around the world (11. Type 2 Diabetes increase the risk of long term damage, dysfunction and failure of various organs especially eyes (blindness), kidney (kidney failure), nerves (diabetic neuropathy), heart (heart attacks) and lower limb amputation [4-7]

Prevalence of metabolic syndrome varies among different populations depending on gender, age, and ethnicity (4). Results from a population study in Prevention of Metabolic Disorders Research Center in Tehran, Iran indicate that among 4018 Iranian subjects 40 years and older, the prevalence of metabolic syndrome was 51.4% (5) hence putting Iranian populations at high risk of complications associated with this syndrome (i.e. cardiovascular diseases). Clinical repercussions of the metabolic syndrome include alterations in glucose and lipid homeostasis of which insensitivity to the actions of insulin is a key feature. This 'resistance' to insulin action is thought to promote a dyslipidemic state in which hepatic gluconeogenesis, glucose output, and VLDL secretion are enhanced. Furthermore, normal post- prandial suppression of adipose tissue lipolysis is compromised in the insulin resistant state leading to a persistent elevation in circulating free fatty acid (FFA) levels. Enhanced FFA mobilization triggers a variety of metabolic deficiencies including further decreases in

insulin sensitivity and subsequent development of hyper insulinemia (6). Current National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines for the treatment of patients with the metabolic syndrome encourage therapies that lower LDL cholesterol and TG and raise HDL cholesterol (1). Primary intervention often involves treatment with statins to improve the lipid profiles of these patients.

The NCEP-ATP III criteria for the metabolic syndrome are based on the presence of 3 or more of the followings: increased waist circumference, elevated triglyceride levels, blood pressure (BP), fasting glucose level, and reduced HDL-C levels. The American Heart Association (AHA) and National Heart, Lung and Blood Institute (NHLBI) groups affirm the overall utility and validity of the NCEP-ATP III criteria and proposed that they should continue to be used with modifications. The modifications include: 1-adjustment of waist circumference to lower thresholds when individuals or ethnic groups are prone to insulin resistance, 2-allowing TG and HDL-C levels and BP to be counted as abnormal when a person is prescribed drug treatment for these conditions, 3-clarifying that elevated BP is defined as an elevation of either systolic or diastolic BP, and 4-reducing the threshold for elevated glucose level from 110 mg per dL or higher to 100 mg per dL or higher.

The International Diabetes Federation (IDF) has proposed clinical criteria similar to those of the NCEP-ATP III with identical thresholds for TG and HDL-C levels, BP, and plasma glucose. The IDF criteria are different in that the waist circumference thresholds are adjusted to different ethnic group and gender and require that increased waist circumference to be considered as an element of the metabolic syndrome because abdominal obesity reflects both concepts of obesity and insulin resistance (7). In the U.S. population, updated NCEP-ATP III and IDF criteria identify essentially the same people as having the metabolic syndrome (7).

The number of people with both Type-1 and Type-2 Diabetes rise from 108 million in 1980 to 463 million in 2019 and 374 million people are at increased risk of developing Type-2 Diabetes. It is the most common public health problem in both developed and developing countries. Over the past decades, there has been a major increase in Type-2 Diabetes prevalence in most regions of the world ns 4). According to NFHS-5 prevalence of Blood sugar levels (BSL) among adult age 15 years and above (BSL - > 140mg/dl) in women and men are 19,3% and 21.8%o respectively in urban and rural (2019- 2020). Thyroid diseases are common problem in the population. (8-11). This small gland located in the neck plays an important role in regulating metabolism, as well as in functioning of a whole range of organs and organ systems. Most of the people with thyroid gland disorders have an autoimmune disease, ranging from primary hypothyroidism, Hashimoto thyroiditis and thyrotoxicosis caused by Graves' disease. According to the functional state, they are divided to euthyroid (normal function), hyperthyroid (overactive

function) and hypothyroid (underactive function). The findings are refered to are refered to as normal, high and low . Hypothyroidism is a most common thyroid disorder in India. Overt Hypothyroidism is the combination of an elevated level of serum thyroid- stimulating hormone (TSH) witha decreased level of serum free thyroxin as compared to the reference ranges in the general population [12j. It can cause an increase in blood pressure, elevated cholesterol levels, decreased fertility, depression, bone deformity and cardiovascular complications (13). It is the 42 million people in India have thyroid disorders and Hypothyroidism is the most common disorder where approximately 1 in 8 women will be affected by thyroid condition at some poimt in their lives. The risk for women is about 10 times higher than men 1s, 19,. The prevalence of Hypothyroidism varies considerably across the general population. There are a number of factors that can influence the prevalence of this condition. For example, the occurrence of Hypothyroidism is affected by differences in the iodine status between populations, with higher prevalence among those with high iodine intake and in severely iodine-deficient populations (14). Prevalence of Hypothyroidism was 10.95% of which 7.48% patients self reported the condition where as 3.47% were previously undetected in Inland cities (15).

3. Patient counselling

It is a process that upgrades the patient's ability to cope with their disease and make informed decisions regarding management and medication. It also helps the patients to change any harmful dietary like cruciferous vegetables; soya products and lifestyle habits like stress management 2). Explain the role of lifestyle modifications includes smoking cessation, weight reduction, proper diet like vegan diet, and regular physical activity and adherence to lifestyle changes can reduce patient disease condition (16). By regular physical activity like yoga not only for physical strength but also for mental wellbeing (17). Diet counseling used to reduce weight, improve sleep quality, strengthen your immune system and reduce symptoms of disease 241. Some studies reveal that patient counseling by pharmacists not only improves the knowledge, attitude and practice of the patients towards their disease management but also increases their quality of life Effective medication counselling has a significant effect on patient counseling. Medication adherence is defined by WHO as the degree to which the person's behavior corresponds with the agreed recommendations from a health care provider with respect to timing, dosage, and the frequency of medication taking during the prescribed length of the time (o. Nonadherence to medication is a common problem associated with increased hospitalization, progression of disease and mortality 291. Levothyroxine (LT4) is a reliable and commonly prescribed drug to treat hypothyroidism. The aim of the substitution therapy is to resolve symptoms and signs of hypothyroidism and maintain the serum thyrotropin (TSH) concentration within a narrow range (18).

Adherence was measured using the Four-item Morisky medication Adherence Scale (MMAS-4) and Eight-item

Morisky Medication Adherence Scale (MMAS-8) 27). Firstly, MMAS-4 is a self reported measure of medication taking behavior. There are two items are assessing the unintentional non- adherence due to forgetfulness and carelessness. The last two items are measuring the intentional non- adlherence stopping medications when feeling better or worse 281. Patients were categorized as 'high' adherers (negative response to all four questions) or 'intermediate/low' adherers (any positive response) Secondly, Eight-item Morisky Medication Adherence Scale (MMAS-8) is also a structured self-report measure of medication-taking behavior; it was developed from a previously validated four-item scale and additional items addressing the circumstances surrounding adherence behavior (30). It has been yerified and substantiated by numerous studies on a global scale with over 110 versions and over 80 translations. Morisky Scale (MMAS-8) has proved to be a valuable resource to address adherence concerns such as forgetting to take medications or discontinuing medications without guidance. If a patient scores higher on the scale, they are evaluated as more adherent. If they score lower on the scale, they are presumed to be struggling with nonadherence. By understanding how the patient the patient scored on the scale, clinicians and health organizations can identify underlying issues that prevent patients from taking their medications correctly (19).

During the past several decades these are the common disorders increased markedly and lead to increase of complications and disturb the quality of life. Upon reviewing literature, adequate research done on Hypertension, Type-2 Diabetes mellitus and Hypothyroidism. However the information on Thyroid disorders (Hypothyroidism) is scarce. So the present study focused mainly regarding counselling on Hypothyroidism because it is one of the most leading problem in India.

4. Management of metabolic syndrome

Clinical pharmacology in management of metabolic disorder: The initial management of metabolic syndrome involves lifestyle modifications, including changes in diet and exercise habits. (20) Indeed, evidence exists to support the notion that the diet, exercise, and pharmacologic interventions may inhibit the progression of metabolic syndrome to diabetes mellitus. [86]Treatment of hypertension had been based on the recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) guidelines, to achieve a goal blood pressure of less than 140/90 mm Hg or, in patients meeting diagnostic criteria for diabetes mellitus, less than 130/80 mm Hg. However, the 2014 report of the Eight Joint National Committee (JNC-8) has led to less stringent recommendations for drug therapy (140/90 mm Hg for most populations, 150/90 mm Hg for patients aged 60 or older), [21] with continued emphasis on the importance of promoting healthy diet and exercise behaviors, as addressed by 2013 guidelines from the American College of Cardiology

Drug utilization studies in metabolic disorder

Diabetes mellitus (DM) is a spectrum of common metabolic disorders, arising from a variety of pathogenic mechanisms, all resulting in hyperglycaemias. It is a serious public health problem because of its high incidence in the population, its complications, mortality, high financial and social cost involve in the treatment and a significant deterioration in the quality of life of the people. (22) The worldwide prevalence of Diabetes mellitus (DM) has risen dramatically over the past two decades from an estimated 30 million cases in 1985 to 425 millions in 2019. Based on current trends, the International Diabetes Federation projects that 592 million individuals will havediabetes by the year 2035. 2 India leads the world with largest number of diabetes subject earning the dubious distinction of being termed as the diabetes capital of the world. 3 The prevalence of diabetes in Indian adults was found to be 2.4% in rural and 4.0% - 11.6% in urban dwellers. 4 India is presently estimated to have 41 million individuals affected by this deadly disease with every fifth diabetic in the world being an Indian. 5 Being a chronic disease with no known curative therapy, the only option for the optimal glucose control is through the strict adherence to medication, diet and life style modifications. And many a times, patients do not adhere to the therapy because of many reasons.(23) The World Health Organization defines "drug utilization" as themarketing distribution, prescription and use of the drugs in a society considering its medical, social, and economic consequences. 6–8 Drug utilization study of anti-diabetic agent is of paramount importance to promote rational drug use and also to make available valuable information for health planning. Yet, research publications regarding this issue in the northeastern part of India are very few in number. (23).

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