



Asteraceae – The Power House Of Diabetic Drugs

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Abstract: The diabetes-associated mortality rate is increasing annually, along with the severity of its accompanying disorders that impair human health. Worldwide, several medicinal plants are frequently urged for the management of diabetes. Reports are available on the use of medicinal plants by traditional healers for their blood-sugar-lowering effects, along with scientific evidence to support such claims. The Asteraceae family is one of the most diverse flowering plants, with about 1,690 genera and 32,000 species. Since ancient times, people have consumed various herbs of the Asteraceae family as food and employed them as medicine. Despite the wide variety of members within the family, most of them are rich in naturally occurring polysaccharides that possess potent prebiotic effects, which trigger their use as potential nutraceuticals. This review provides detailed information on the reported Asteraceae plants traditionally used as antidiabetic agents, with a major focus on the plants of this family that are known to exert antioxidant, hepatoprotective, vasodilation, and wound healing effects, which further action for the prevention of major diseases like cardiovascular disease (CVD), liver cirrhosis, and diabetes mellitus (DM). Moreover, this review highlights the potential of Asteraceae plants to counteract diabetic conditions when used as food and nutraceuticals. The information documented in this review article can serve as a pioneer for developing research initiatives directed at the exploration of Asteraceae and, at the forefront, the development of a botanical drug for the treatment of DM.

Keywords: Asteraceae, diabetes, drug development.

Introduction: Diabetes mellitus (DM), or insulin-dependent diabetes, is a metabolic disorder in which the blood glucose level increases above the normal threshold. In this condition, the β -cells of the islets of Langerhans of the pancreas are either unable to produce insulin or their glucose-utilizing ability is inhibited. In some cases, the cells may resist insulin uptake and utilization. This disorder is a chronic illness with a global social and economic impact. Low insulin levels affect several tissues, like skeletal muscles, adipose tissues, the kidneys, and the

liver, to such an extent that they downregulate the signal transduction system and the expression of associated genes. Hyperglycemia is often accompanied by several symptoms, including extreme weight loss, polyuria, and polyphagia, and under severe conditions, it can lead to ketoacidosis, which may result in death (Kharroubi and Darwish, 2015). According to the World Health Organization (WHO), around 422 million adults suffered from DM in 2014, and it was the ninth leading cause of death globally in 2019, accounting for approximately 1.5 million deaths. Interestingly, DM is a “silent” illness that can worsen due to negligence and insufficient healthcare. Approximately 47% of diabetic individuals are unaware of their condition (Adailton da Silva et al., 2018). As a result, a DM diagnosis is often met with feelings of shock and denial, which further leads to a reluctance to undergo treatment involving important lifestyle-related changes. Many synthetic drugs are

available for managing and treating type-2 DM (DM2); however, they often fail to address the complications of the disease, and most available therapies seem insufficient. Most patients require regular insulin administration, and around 75% develop CVD (Goje et al., 2014).

Obesity and DM2 have long been linked, which explains the high prevalence of DM2 in many developed countries, with DM2 also being a substantial risk factor for CVD. Because obesity is frequently associated with hypertension and dyslipidemia, many high-risk obese patients have a confluence of metabolic and cardiovascular risk factors. Thus, obesity (especially in its high-risk forms) is a standard driver of altered metabolic activities that lead to DM and cardiovascular risk factors that can be targeted with pharmacotherapies (Flegal et al., 2007). The relationships between obesity and high-risk cardiometabolic risk variables, such as DM, and the consequences of cardiovascular disease have been depicted in Figure 1.

The prevalence of obesity is a risk factor for developing DM2 (Flegal et al., 2007). Numerous studies using upper body, abdominal adiposity anthropometric indices, or direct imaging measurements (CT or MRI) have shown that an enlarged waistline, a higher waist-to-hip ratio, or higher levels of visceral adipose tissue (VAT) at any body mass index (BMI) level significantly raise the risk of developing DM2, in addition to overall obesity (Després, 2012). Patients with DM2 tend to be overweight and have a higher VAT than those with a similar body mass index who do not have DM. While having each of these conditions individually increases the risk of cardiovascular consequences, having both visceral or severe obesity and DM2 should exponentially increase that risk. The enhanced risk of developing cardiovascular problems and heart failure due to the increasingly common coexistence of DM2 and high-risk forms of obesity poses complex management issues. Insulin resistance, which may be partially mediated by obesity, DM2, and cardiovascular risk, is associated with ectopic and visceral adiposity. CVD mortality risk has been linked to metabolic syndrome and insulin resistance (Li et al., 2007).

The lack of available treatments and economical insufficiency to procure expensive treatments have led scientists and researchers to resort to alternative medicine. As such, botanical drugs, herbal medicines, and other dietary supplements may be suitable for treating DM.

In the present stressful world, a balanced diet and healthy lifestyle are of utmost importance. Foods fortified with high amounts of antioxidants, vitamins, and minerals are gaining tremendous importance. According to Health Line, fortified foods refer to items low in trans-fat but rich in vitamins, minerals, probiotics, fiber, and metabolites with high nutritional value and substantial health benefits. A prominent issue here is that “nutraceuticals” refer to the active components present in functional foods that can be extracted, purified, and concentrated for use and have different usages apart from being “functional foods.” An online search on PubMed and Google Scholar demonstrates that diet management is an essential parameter for preventing and curing diseases such as CVD, DM, hypertension, obesity, and thyroid disorders. A large body of clinical evidence suggests that DM2 and its associated complications can be prevented. The risk of disease can be avoided by the consumption of foods that are rich in antioxidants, have reasonable glycemic control, regulate blood pressure, promote the growth of favorable gut microbes, lower inflammatory cytokine secretion, and activate the production of “good” enzymes and hormones (Alkhatib et al., 2017). It is interesting to note that the traditionally used Mediterranean diet (MD) is considered one of the healthiest diets for human longevity and the prevention of chronic illnesses like DM, as it is rich in secondary metabolites and other components that are recommended for the prevention of DM (Rivera et al., 2010; Mirmiran et al., 2014). Many plant families like Zingiberaceae (e.g., *Alpinia galanga* (L.) Wild.), Lamiaceae (e.g., *Salvia officinalis* L.), Caryophyllaceae (e.g., *Corrigiola litoralis* sub sp. *foliosa* (Pérez Lara) Devesa), and many others have been consumed traditionally for many generations due to their many health benefits.

For a long time, plants have had a strong foothold in traditional medicine and form the basis of modern-day medications. Age-old medicine practices like Ayurveda and Unani have practitioners who rely on different plants and their parts to treat various diseases, and these treatment systems are still practiced in Southeast Asia. However, the problem with traditional medicines is the lack of documentation, authenticity, and

scientific evidence. Most of the 'bej, 'kobiraj,' or local healers have learned the art and knowledge of traditional healing from their ancestors, having been handed down as a legacy. According to the WHO, most of the global population relies on herbal medicines and drugs to treat diseases, from wound healing to CVD treatments.

Interestingly, some of these medicinal plants find their use as one or more culinary spices and are consumed as food. One of the most common examples in this respect is the Zingiberaceae family, the natural 'pharmacy' of the plant kingdom and the rich flavoring ingredient of the kitchen. *Alpinia nigra* (Gaertn.) Burt, a lesser explored member of this family, is traditionally used to treat gut infections caused by *Fasciolis buski* and is also used to prepare delicacies like 'eromba' and 'deragong' in Manipur and Tripura, respectively (Swargiary et al., 2013; Swargiary and Verma, 2015; Chakrabarty et al., 2019). Asteraceae is one such family of medicinal plants that has not been explored much but houses a wide range of plants to treat diseases.

Asteraceae, or Compositae, also known as the 'daisy' family, is a large family of angiosperms that harbors around 32,000 plant species with a cosmopolitan distribution, growing in all regions of the world except Antarctica. These plants have been used as medicines and as part of the human diet for ages. This family includes some well-known medicinal plants like lettuce, chamomile, and dandelion, as well as ornamental plants like daisies, sunflowers, chicory, and dahlias (Aboul Ela et al., 2012). Some of these plants and their parts are caffeine-free, extremely rich in vitamin C, E, and organic acids, and commonly used in salads and sandwiches. As such, these plants can be widely cultivated as sources of functional foods. Different species of Asteraceae have been reported to exhibit other pharmacological properties that can be attributed to the presence of large quantities of phytochemicals and secondary metabolites, including essential oils, lignans, tannins, flavonoids, alkaloids, phenolic acids, and saponins. Most of these plants have many sesquiterpene lactones, which impart a bitter taste (Djellouli et al., 2013). Secondary metabolites are responsible for antioxidant, anticancer, and antimicrobial properties; hence, the plants of the Asteraceae family can be exploited for the treatment of certain serious disease like CVD, hypertension and DM.

The present review aims to bridge the gap in existing literature regarding the role of several members of the family Asteraceae, particularly in preventing DM2 and diabetic wounds, and their application as fortified foods. Extensive literature is available on the role of medicinal plants in the management of lifestyle-related disorders. But this review is novel as it focuses explicitly on managing DM2 using different members of the Asteraceae family alone. Not only that, the utilization of secondary metabolites and bioactive compounds from this family as dietary supplements and fortified food is highlighted, specifically focused on the management of DM. In Section 4, the role of different members of the Asteraceae in wound healing has been described in detail. Section 5 describes the untapped and identified compounds from Asteraceae against DM. Sections 6 and 7 discuss the prospects of research in Asteraceae (in search of novel bioactive compounds to be used as medicines and fortified foods).

Safety: Safety concerns are another major issue with herbal drugs. The effects can be severe and detrimental if the appropriate dosage is not determined, as active compounds are toxic at high doses. The administration, distribution, metabolism, and excretion (ADME) of a compound that may act as a drug needs to be studied as it determines the bioavailability or fate of the compound; this stands true for all compounds (synthetic and herbal) that can be developed as drugs in the future. The FDA, United States, has designed a set of guidelines for all pharmaceutical companies and drug manufacturers to strictly adhere to for proper manufacturing, safety, and toxicity labeling. This ensures that all information is available to consumers to make an informed choice or purchase. However, several countries do not have appropriate regulations for quality control and risk assessment of bioactive compounds from natural sources. Coupled with the lack of consistency, misinformation between different countries across the globe can lead to disastrous effects and prevent the establishment of plant-based compounds as therapeutic products and nutraceuticals.

Conclusion and prospects: Lifestyle-related disorders have become commonplace in today's world owing to the hectic and sedentary lifestyle, stress, and lack of awareness or consciousness of one's health. Asteraceae is traditionally used worldwide to treat various diseases, including infections, wound healing, liver dysfunction, and other disorders. Complex secondary metabolites play a major role in bringing out these activities. Despite the excessive scientific studies in the search for new antidiabetic drugs, more work is needed to yield potent, commercially available drugs based on medicinal plants. Indeed, the scientific community and pharmaceutical companies have failed to provide the required attention to this plant family to explore therapeutic products, although a Nobel Prize has already been awarded. Although several plants from this family were extensively studied, some of the species important in traditional medicine have still hardly been studied for their bioactivity. Therefore, the present review aims to encourage in-depth exploration of different members of the Asteraceae family for the treatment of DM, guided by folk and traditional knowledge. The daisy family exerts antioxidant, hepatoprotective, vasodilation, antidiabetic, and wound healing effects, which further prevent major diseases like CVDs, liver cirrhosis, and DM. Most of these studies are still in the preliminary stages of in vitro and in vivo experiments, while clinical trials are lacking. No doubt, a few studies related to flavonoids and their mode of action in the treatment and management of DM are available, but pharmacokinetics/ pharmacodynamics in laboratory animals and clinical trials are warranted to investigate their effects, including the mechanisms of action.

The information documented in this review article can serve as a pioneer for developing research initiatives directed at the exploration of the Asteraceae family at the forefront of developing a botanical drug to be used as a treatment for DM. With a shift towards plant-based and herbal products for nutrition and wellbeing, there is a high chance that consumers may easily opt for natural products for food and medicine in the long run.

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