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Anti-diabetes role of ginger

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Abstract

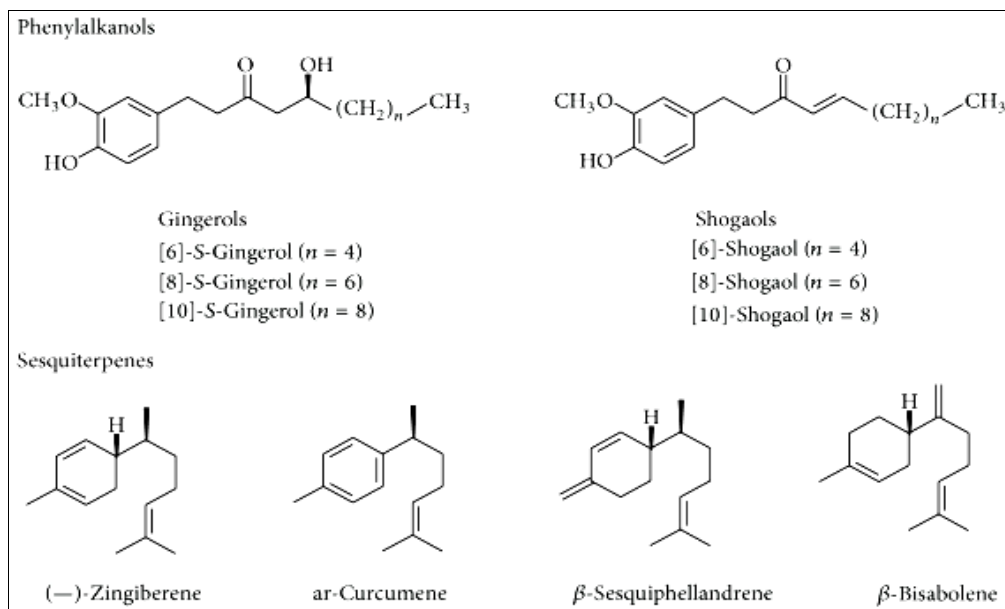
A flowering plant known as ginger is utilized for both culinary and medicinal purposes and traditional healing. Ginger (*Zingiber officinale*), a spice used in Chinese and Ayurvedic traditions to treat diseases ranging from gingivitis to asthma, contains many antioxidant compounds that are thought to exert strong anti-inflammatory effects by inhibiting cyclooxygenase, inducible nitric oxide synthase, and lipoxygenase, as well as suppressing prostaglandin synthesis. Ginger is rich in bioactive components that promote the prevention and treatment of chronic conditions like heart disease, cancer, and Type 2 diabetes, are inexpensive and have no side effects. India produced 4.3 million tonnes of ginger worldwide, accounting for 43% of the total. Nepal, China, and Nigeria all had sizable productions. It is an abundant source of phytochemicals and antioxidants with anti-inflammatory, antibacterial, and anticancer activities is ginger (*Zingiber officinale*). For many years, people have used ginger both as a condiment and to treat illnesses. However, research on the antioxidant and free-radical scavenging properties of processed ginger is scarce. Using 1,1-Diphenyl-2-picrylhydrazyl (DPPH), Radical-Scavenging Activity, and Ferric Reducing Antioxidant Power, the study's goals were to ascertain the effects of processing on ginger's total phenolic and flavonoid content as well as its antioxidant capacity (FRAP).

Keywords: Ginger, *Zingiber officinale*, anti-inflammatory, anti-diabetic, antioxidant

Introduction

Diabetes mellitus is dispersing at an alarming rate over the world as a result of changes in lifestyle and living conditions. According to figures provided by the International Diabetes Federation (IDF), there were 415 million diabetic people in 2015, and 10% of adults would have the disease by 2030. In 2010, 6.4% of adults worldwide were affected by diabetes mellitus, which has pandemic proportions (Blumenthal *et al.*, 2011) [5]. Type 1 and type 2 diabetes mellitus are the two main subtypes and are distinguished by chronic hyperglycemia brought on by impaired insulin action/secretion. More than 90% of cases of diabetes are type 2 and are characterised by lipid and carbohydrate metabolic disorders. Reducing the risk of micro- and microvascular disease in diabetic patients requires effective control of hyperglycemia. The effectiveness of the currently available hyperglycaemia medications has been limited by their side effects (Akhani *et al.* 2004) [1]. This has prompted ongoing efforts to investigate powerful medicines for the management of diabetic mellitus. The benefits of ginger in managing metabolic illnesses and related consequences are less well-known, though (Wohlmuth *et al.*, 2005) [30]. Here, we go over the recognised effects of ginger on diabetes mellitus and give some insight into the main ingredients and how they work.

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Numerous research have looked at the effectiveness of ginger in controlling hyperglycemia *in vitro*, *in vivo*, in cell and animal models, as well as in clinical trials. Investigations into the mechanisms of action and active principles have also been made. In a STZ-type 1 diabetic rat model, oral administration of an ethanolic extract of ginger (800 mg/kg) was found to dramatically lower fasting blood glucose levels after one hour of treatment (Sharma and Shukla, 1977) [29]. After four hours, the impact peaked, with doses of 100 to 800 mg/kg of ginger causing a 24% to 53% decrease in blood glucose. Another study found that a single dosage of ginger juice reduced acute hyperglycemia caused by 5-hydroxytryptamine (5-HT), indicating the role of 5-HT receptors in glycaemic regulation. In rats with STZ diabetes, ginger therapy resulted in a considerable reduction in the area under the plasma glucose level curve and an increase in the area under the insulin curve during the oral glucose tolerance test. A chronic metabolic disease called type 2 diabetes mellitus is linked to insufficient exercise and excessive calorie intake. According to a study on rats fed a high-fat diet (HFD), ginger has been shown to be protective against the development of different metabolic syndrome characteristics, which increases the risk of type 2 diabetes. The significant increases in body weight, serum glucose, insulin, total cholesterol, LDL cholesterol, triglycerides, free fatty acids, and phospholipids brought on by a high-fat diet were significantly reduced after treatment with an ethanolic extract of ginger at doses of 100, 200, and 400 mg/kg for six weeks. Ginger powder (200 mg/kg) was administered orally to treat metabolic syndrome symptoms in a nicotinamide and low dosage STZ-induced type 2 diabetic rat model, including a reduction in blood glucose, total lipid, and cholesterol levels. Ginger's effects on typical animals weren't always predictable. One hour after ginger extract administration, a glucose-lowering effect was reportedly seen. A standardised dry ginger ethanol extract with 1.9 w/w of gingerol that was prepared in maize oil EV.EXT 33 (25, 50, and 100 mg/kg) did not, however, have any influence on blood glucose levels in healthy rats three hours after administration. Furthermore, neither blood insulin levels nor levels of cholesterol and triglycerides were impacted in rats given fresh ginger juice for six weeks. Type 2 diabetes mellitus (T2DM) is a significant risk factor for diabetes that is raised by about five times by metabolic syndrome (MetS), and it affects up to one-fourth of adults worldwide (Grundy S. M *et al.*, 2005) [15]. The public's health was significantly

jeopardised by the diseases. Raised blood sugar, impaired insulin sensitivity, obesity, dyslipidemia, and hypertension are shared symptoms in patients with T2DM or MetS, and these symptoms frequently co-occur rather than develop separately (Kaur J, *et al.*, 2014) [21]. Currently, the majority of clinical treatment focuses on pharmacological symptom control; however, the adverse effects of these medications, particularly for long-term administration, have raised significant public concerns. There is an urgent demand for alternative therapies with fewer side effects. The herbaceous perennial plant known as ginger, or *Zingiber officinale* Roscoe, is used as a spice all throughout the world due to its distinct pungency and distinctive aroma. In addition, ginger has long been a popular medicinal herb in both Indian Ayurvedic Medicine and traditional Chinese Medicine (Panahi Y, *et al.*, 2012) [25]. It is used to treat primary dysmenorrhea, arthritis, nonalcoholic fatty liver disease, stomachaches, and nausea brought on by chemotherapy and pregnancy. According to Wang *et al.*, ginger has numerous targets and pathways that make it a promising treatment for T2DM and MetS. These key bioactive components, which include gingerols, shogaols, zingerone, and paradols, may be the cause of this beneficial impact. However, there was conflicting information: (Bordia *et al.*, 1997) [6] found that after ingesting 4 g of ginger powder for three months, coronary artery disease patients' blood glucose or lipid levels did not change. Depending on the preparation technique, the region of production, or the storage conditions, the chemical makeup of ginger products can vary, which could explain the discrepancy in the results. Our systematic review sought to summarise the compelling data from recent research to explain ginger's effectiveness on T2DM and MetS components (Kaur J, *et al.*, 2014) [21]. *Zingiber officinale* Roscoe, also known as ginger, is a member of the ginger family and is widely grown in tropical and subtropical regions for both culinary and medicinal applications. Ginger is utilised as an ingredient in the food and beverage sector for its flavour and scent. Fresh ginger's chemical makeup differs depending on the variety or cultivar, the region in which it is grown, the extraction technique, and the processing technique. With a retail sales volume of roughly United States (US) \$1.38 million in 2010, a 17.4% increase over the previous year, ginger is among the top 20 herbal supplements in the USA. Ali, Blunden, Tanira, and Nemmar reviewed the pharmacological, phytochemical, and toxicological properties of ginger, including its effects on a

number of metabolic and age-related degenerative diseases as well as its anti-inflammatory, antioxidant, anti-lipidemic, immuno-modulatory, and anti-tumorigenic properties. The most common forms of ginger traded on the global market are powders and extracts. The primary characteristics of ginger that is suitable for export are its scent or pungency, which is generated from important chemical constituents such as volatile essential oils and non-volatile oleoresin. The bioactive chemicals found in the non-volatile pungent compounds include gingerols, shogaols, zingerone, and paradols, while the volatile essential oils contain zingerberene, curcumene, and farnesene. These elements give ginger its distinctive spicy flavour. Gingerol is the most prevalent non-volatile molecule in ginger, but it also contains a variety of bioactive substances such as diarylheptanoids, 3-dihydroshogaols, and other methyl ether derivatives that are plentiful in the plant. Gingerol is dehydrated during thermal processing to produce shogaol, which gives ginger its distinctive pungency. The pace at which gingerol is converted to shogaol may also depend on pH. Processing alters the chemical composition of ginger by removing certain compounds, particularly cyclic ones, and may also cause new compounds to arise due to molecular rearrangement, oxidation, or degradation. The availability of some chemicals is impacted by various dehydration techniques such as microwave drying, freeze drying, air drying, and vacuum drying. According to a study by Chan, Lim, Wong, Lim, Tan, Lianto, & Yong on the effects of thermal and non-thermal drying procedures on the antioxidant capabilities, total phenolic content, and ferric-reducing ability of ginger leaves and tea, some of the drying methods led to a drop in these qualities. The aim of this study was to analyze ginger extracts from both fresh and processed forms in order to determine their total phenolic and flavonoid content, radical-scavenging activity (DPPH), and ferric-reducing antioxidant power (FRAP).

Ginger inhibits enzymes in carbohydrate metabolism

Amylase and glucosidase are the two main enzymes in charge of the carbohydrate metabolism linked to hyperglycemia and type 2 diabetes. On sequential extracts of ginger with hexane, ethyl acetate, methanol, 70% methanol-water, and water, an *in vitro* enzyme inhibition investigation was carried out. The strongest -glucosidase and -amylase inhibitory activity was demonstrated by the ethyl acetate extract, with IC₅₀ values of 180 mg/mL and 980 mg/mL, respectively (Priya Rani M, *et al.*, 2011) [26]. Other extracts did not show any effects. The phenolic concentration of gingerol and shogaol in these extracts was discovered to be linked with the activity of ginger against these two enzymes. However, -glucosidase but not -amylase were only slightly inhibited by an aqueous extract of Jamaican ginger. These findings may be explained by the ginger water extract's low total phenolic component content. According to *in vivo* research on rats, pancreatic lipase, amylase, trypsin, and chymotrypsin activities dramatically enhanced following long-term (8 week) ginger feeding. The activity of these enzymes were, however, reduced in the pancreas after a single dose of ginger, whereas amylase and sucrase were enhanced in the intestinal mucosa.

Ginger increases insulin release and sensitivity

Defects in insulin release or/and sensitivity are hallmarks of diabetes mellitus. The decrease in blood glucose level was seen to be followed by a decrease in insulin concentration in the STZ-induced type 1 diabetic rat model. It has been demonstrated that ginger controls insulin release (Rossini AA *et al.*, 1977) [28]. In INS-1 rat pancreatic -cells cultured *in vitro*, ginger extract increased insulin secretion. It's interesting

to note that this effect was stronger when exogenous serotonin was present. A glucose tolerance test performed in humans further shown that this ginger extract improved plasma insulin levels in addition to lowering blood glucose levels. [6]-gingerol demonstrated a protective effect on pancreatic -cells and recovered the plasma insulin level in type 2 diabetic rats that had been exposed to arsenic (Junod A *et al.*, 1969) [19]. The interaction of ginger with the 5-HT₃ receptor may be the mechanism underlying this effect. With the potency order [6]-shogaol [8]-gingerol [10]-gingerol [6]-gingerol, it was discovered that gingerols and shogaols can operate on the 5-HT₃ receptor-ion channel complex by binding to a modulatory location different from the serotonin binding site. Further analysis is still needed to determine the importance of this process.

Methods

The Cochrane Handbook's recommendations were followed in conducting this systematic review and meta-analysis, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to report the findings. It had a PROSPERO registration. CRD42017069241 is the registration number, according to <https://www.crd.york.ac.uk/PROSPERO>.

Search strategy

Two authors (HC and SZS) independently searched the following electronic databases from the database's creation to May 19, 2017: PubMed, Embase, the Cochrane Library, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), and Wanfang Database (Higgins J, *et al.*, 2011). [16] Thesaurus terms and free terms made up the list of search terms. Randomized trials were found using a sensitivity-maximizing search method in PubMed. The search terms were modified in accordance with the demands of the filters for randomised controlled trials that were specific to the database (RCTs). There is a list of all possible PubMed search keywords. By looking through the literature in the reference lists and manually searching through pertinent publications in the field of diabetes and MetS, the search was supplemented with potentially relevant papers.

Inclusion and exclusion criteria

We included studies in which the participants had T2DM and/or at least one component of MetS according to the International Diabetes Federation standards, the intervention was restricted to ginger alone; and the study was conducted as a randomised controlled trial in order to estimate the effects of ginger on T2DM and components of MetS. These criteria were used to exclude people: a non-standard diagnosis; the control group receiving care other than a placebo. When there was more than one endpoint in a study, the longest intervention period was used. All relevant data about the outcomes of interest were extracted and used in the case of several publications based on the same trial. Correspondence, case reports, and editorials were not included.

Study selection

Based on the PRISMA proposal process, the study was chosen. The duplicate studies were first eliminated, and a list of possibly suitable articles was created after two reviewers (HC and SZS) independently assessed the titles and abstracts of all retrieved literatures according to the inclusion and exclusion criteria. Two reviewers (HC and SZS) then looked at the entire texts of these possible studies for future selection. Conflicts were settled through consensus (Moher D, *et al.*,

2009) [23]. Throughout the entire procedure, JZ, a third reviewer, was available for mediation. To ensure eligibility for potential publications, we contacted the relevant authors if the literature was not yet available in the publication and could not be excluded. Up to two times within three days were made contact with study authors.

Data extraction

Data extraction was carried out independently by two reviewers (HC and SZS) using a specified standard form. The disputes were resolved after consulting a third party (JZ). We gathered data as follows for each included article: (1) First author's name, year and place of publication, sample size, population details, intervention techniques and doses, length of follow-up, and study design; Serum triglyceride (TG), serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), fasting blood glucose (FBG), glycosylated haemoglobin (HbA1c), homeostasis model assessment-insulin resistance index (HOMA-IR), and body mass index are two outcomes of interest (BMI). Before they were integrated, all of the value scales were unified.

Assesment of risk of bias

Using the Cochrane Collaboration "Risk of bias" assessment tool, we evaluated the risk of bias for each included study. The Cochrane Handbook's standards for evaluating the risk of bias were presented in the following specific domains: attrition bias (incomplete outcome data), reporting bias (selective reporting), performance bias (blinding of participants and staff), detection bias (blinding of outcome assessment), and other sources of bias (Higgins J, *et al.*, 2011) [16]. Each item was given a "yes," "no," or "unclear" rating from two reviewers (HC and SZS), equivalent to a "low risk," "high risk," or "unclear risk" of bias. Consultation with the third party was used to address disagreements in the

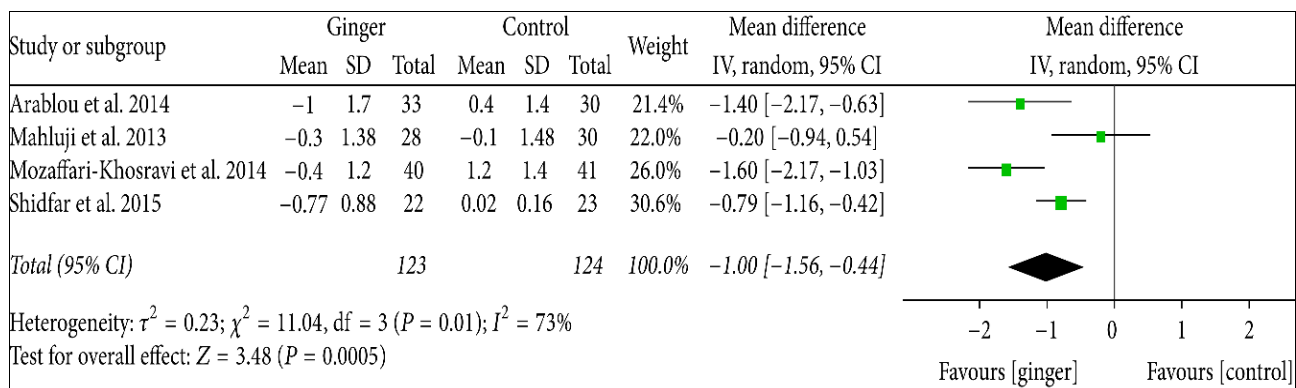
assessment (JZ). Rev Man software was used to conduct each evaluation (V.5.3.5).

Data synthesis and analysis

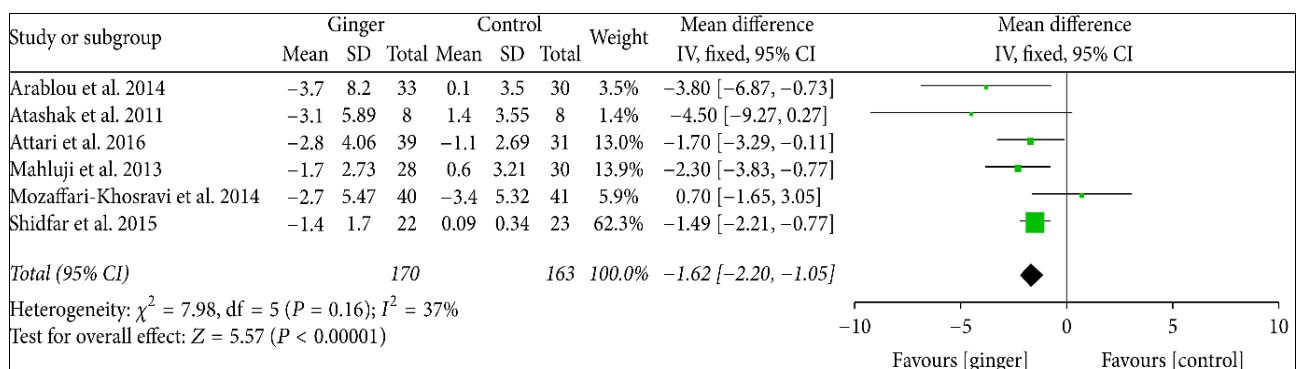
The Cochrane Collaboration's Review Manager 5.3.5 application was used to evaluate the data and create forest plots. When there was no statistical heterogeneity, a fixed-effect model was used; otherwise, a random-effect model was utilised (Riley RD, *et al.*, 2011) [27]. The I2-test statistic and degree of freedom P value were used to evaluate heterogeneity. Values of P0.10 or I2>50% indicated significant heterogeneity, and the random-effect model's findings were published (Higgins J. *et al* 2002) [16]. Additionally, when information on the desired outcomes was available from at least two studies, a meta-analysis was conducted. For continuous variables, the weighted mean difference (WMD) with a 95% confidence interval (CI) was calculated. A P 0.05 significance threshold was used. When there were potential discrepancies across studies, subgroup analysis was carried out based on the categories of disease.

Effects of ginger on glucose control and insulin sensitivity

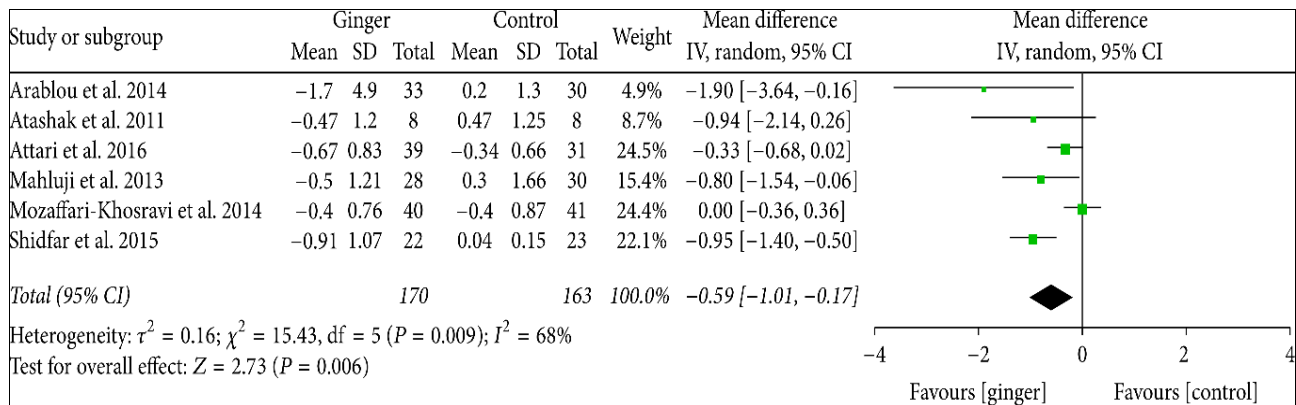
Compared to a placebo, ginger powder could dramatically increase insulin sensitivity and blood glucose levels. Four studies provided data on the average changes in HbA1c (% overall). WMD and 95% CI of HbA1c showed a significant change following ginger administration against placebo (1.00; 95% CI: 1.56, 0.44; P 0.001). Six trials examined the mean changes in fasting insulin concentrations (IU/ml), and a significant difference between the ginger groups and the control groups was found (1.62; 95% CI: 2.20, 1.05; P 0.001). Additionally, six research examined insulin sensitivity using the HOMA-IR index. The pooled net change indicated a clear improvement in insulin sensitivity (0.59; 95% CI: 1.01, 0.17; P 0.001).



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Adverse effects

According to the study, consuming ginger powder preparations on a regular basis for an extended period of time won't have any major negative effects or issues that typically arise when taking hypoglycemia or hypolipidemic medications. Only one study out of the 12 studies considered in the current systematic analysis reported a minor adverse event. One occurrence of early-stage heartburn in the ginger group in this RCT, while the remaining patients experienced no discomfort. In other words, ginger was generally regarded as both a food on the FDA's "generally regarded as safe" list as well as a safe medicinal plant based on the research that was included.

Limitations

The current review may have a few drawbacks worth mentioning. First of all, despite using a broad search method to reduce publication bias, some linguistic bias may still exist because this meta-analysis only included articles written in English or Chinese. Additionally, the validity of the results was constrained by the limited body of literature and overall sample size. Additionally, because most trials' interventions lasted for a brief time, it was difficult to find a statistically significant improvement in BMI. Therefore, to investigate the effects of ginger on T2DM and elements of the MetS, properly planned, sufficiently powered, and longer-term RCTs are required.

Future outlook and perspective

The science of "reverse pharmacology" (B. Patwardhan and A. D. B. Vaidya, 2010) [8] can be used to herbal natural product medical research. While the allopathic pharmaceutical drug discovery approach begins with a new molecule (a chemical molecule isolated from a natural product or synthesized chemically) and is followed by cellular and animal studies leading to clinical investigation in phase 1-4 clinical trials, reverse pharmacology has as its foundation traditional knowledge of use and safety accumulated over hundreds or even thousands of years. Modern pharmacological studies relevant to diabetes management can validate extensive traditional knowledge on ginger, emphasizing the chemical nature of ginger, its effects on hyperglycemia and hyperlipidemia underlying insulin resistance, and inflammatory responses in animal models and *in vitro* cell studies as well as detailed investigations into the mechanisms underlying the observed biological actions. However, this information is insufficient to give proof for the safety and efficacy of a natural substance and need more inquiry. Studies on the mechanisms of biological effects

provide for a better knowledge of the elements behind the medicine's safe usage, such as interactions with other medications or dietary considerations. If the sum of these findings validates and explains the conventional applications, a clinical investigation in volunteers or patients may be warranted for the planned outcome.

Conclusion

This study provided an update on the anti-diabetic properties of ginger (Zingiberaceae family). Despite the availability of multiple *in vivo* and *in vitro* data, clinical (human) trials were few. The dosages and results varied, as did the mode of action by which the anti-diabetic benefits were mediated. Although these results suggest that ginger has anti-diabetic or hypoglycemic properties, the dosages and outcomes varied; more significantly, the mechanisms of action by which anti-diabetic benefits are mediated were highlighted. According to these research, ginger has anti-diabetic benefits through restorative actions on pancreatic β -cells, enhancing insulin sensitivity, insulin-like action, and peripheral glucose utilization. Enhanced hepatic glycogen synthesis via increased glycogen regulating enzyme expression in the liver, inhibition of carbohydrate metabolizing enzymes, stimulation of pancreatic insulin release, and inhibition of hepatic glucose production are some of the other ways. However, further research, particularly in humans, is required, and the oral safety of the different extracts under continuous use must be proven, especially because ginger is one of the spices widely recognized as safe.

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