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A Scoping Review on Pathogenesis of Metabolic Syndrome and its Management Through Unani Herbal Drug 'Darchini' (*Cinnamomum zeylanicum*)

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Abstract

Background:

Metabolic Syndrome (MetS), also called Syndrome X or Insulin Resistance Syndrome, is a growing global concern linked to cardiovascular disease and type 2 diabetes mellitus. It is characterized by insulin resistance, dyslipidemia, hypertension, obesity, and systemic inflammation. Lifestyle modification and pharmacotherapy remain the primary management strategies but are limited by side effects and adherence issues. Unani medicine provides holistic approaches, among which Darchini (*Cinnamomum zeylanicum*) is noted for its therapeutic versatility.

Objective:

This review evaluates the etiopathogenesis of MetS and the pharmacological potential of *Cinnamomum zeylanicum* in its management.

Methods:

Databases including PubMed, Scopus, and Google Scholar were searched for studies published between 2000 and 2024. Eligible studies comprised randomized controlled trials, observational studies, systematic reviews, and reviews investigating *Cinnamomum zeylanicum* in relation to glucose metabolism, lipid profiles, blood pressure, inflammation, and obesity.

Results:

Metabolic Syndrome results from insulin resistance, visceral adiposity, oxidative stress, and chronic inflammation. *Cinnamomum zeylanicum* improves insulin sensitivity, reduces fasting glucose and HbA1c, and enhances glucose uptake. It lowers total cholesterol, triglycerides, and LDL while increasing HDL. Its antihypertensive effects are mediated by enhanced endothelial nitric oxide production and vascular protection. Antioxidant and anti-inflammatory actions attenuate oxidative stress and cytokine-induced injury, while anti-obesity properties modulate adipogenesis and lipid metabolism. These combined effects directly target the core metabolic dysfunctions of MetS.

Conclusion:

Cinnamomum zeylanicum demonstrates significant potential as an adjunctive therapy for MetS, addressing multiple pathophysiological pathways. Further large-scale clinical trials are required to establish standardized dosages, confirm efficacy, and ensure long-term safety.

Keywords: Metabolic Syndrome, Obesity, Insulin resistance, Unani medicine, Herbal drugs

Introduction

Metabolic Syndrome also known as Syndrome X or Insulin Resistance Syndrome is a significant global health concern with a rising prevalence. It consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease and diabetes mellitus. The condition is primarily linked to lifestyle factors, genetic predisposition, and systemic inflammation [1–4]. Current medical management involves lifestyle modification and pharmacotherapy, but these interventions may have limitations due to side effects and patient compliance issues.

Unani medicine, an ancient system of healing, offers herbal remedies that address the underlying causes of Metabolic Syndrome through detoxification, metabolism regulation, and organ-specific actions. Darchini (*Cinnamomum zeylanicum*), commonly known as Cinnamon, has been extensively used in Unani medicine for its medicinal properties.

This scoping review aims to consolidate evidence on the pathophysiology of Metabolic Syndrome and the therapeutic potential of Darchini (*Cinnamomum zeylanicum*) in its management.

Methods

A comprehensive literature search was conducted using databases such as PubMed, Scopus, and Google Scholar. The selection criteria included peer-reviewed articles, reviews, and clinical trials that address Metabolic Syndrome's pathogenesis and management. Studies also included randomized controlled trials (RCTs), observational studies, and systematic reviews published in peer-reviewed journals between 2000 and 2024. The inclusion criteria focused on human studies investigating the effects of *Cinnamomum zeylanicum* on Metabolic Syndrome parameters such as glucose metabolism, lipid profiles, blood pressure, and inflammation.

Etiopathogenesis of Metabolic Syndrome

Metabolic Syndrome (MetS) results from a complex interplay of genetic, environmental, and metabolic factors. The primary pathophysiological mechanisms include:

Insulin Resistance:

A hallmark of Metabolic Syndrome is the insulin resistance in which normal insulin concentration does not adequately produce a normal insulin response in target tissues such as adipose tissue, muscle and liver. The impaired glucose uptake by the target tissues results in hyperglycaemia and to overcome the hyperglycaemia pancreatic beta cells secrete more insulin (hyperinsulinemia)[5]. Persons with Metabolic Syndrome have a significantly higher risk of developing type 2 diabetes mellitus [6]

Dyslipidemia:

Insulin resistance disrupts normal lipid metabolism, leading to increased hepatic production of VLDL and impaired clearance of triglyceride-rich lipoproteins. These disruptions result in atherogenic dyslipidemia, marked by the accumulation of VLDL, small dense LDL, and low HDL-C, which accelerates the development of atherosclerosis [7]

Hypertension:

Insulin resistance and the compensatory hyperinsulinemia that accompanies it over time are posited to not only result in the development of diabetes but also to contribute to the development of elevated blood pressure and hypertension [8]

Under normal conditions, insulin promotes vasodilation by stimulating nitric oxide (NO) production in endothelial cells via the PI3K-Akt pathway. However, in insulin-resistant states, this pathway is impaired, leading to reduce NO production and endothelial dysfunction, a key feature of hypertension. Simultaneously, insulin resistance activates the MAPK (Mitogen-Activated Protein

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Kinase) pathway, enhancing the activity of vasoconstrictors such as endothelin-1 (ET-1) and angiotensin II (Ang II), further elevating blood pressure [7], [8].

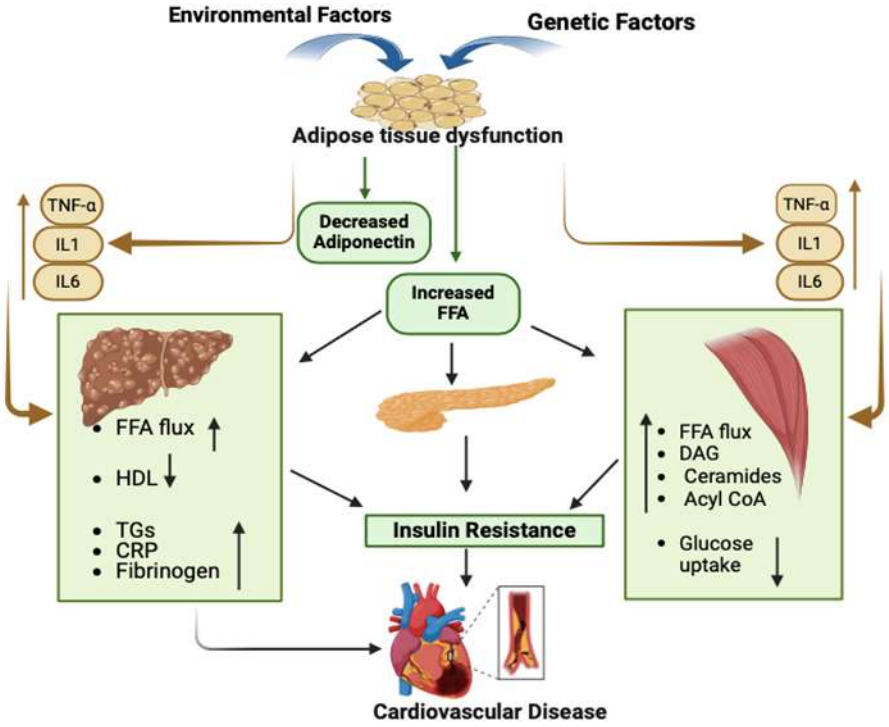
Obesity and Inflammation:

Obesity is associated with chronic low-grade inflammation in adipose tissue. Obesity-related inflammation is associated with the increased release of chemotactic factors, anti-inflammatory adipokines, pro-inflammatory adipokines and pro-inflammatory cytokines [9] The proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, are found to be deregulated in MetS. These proinflammatory cytokines are mainly produced by the macrophages infiltration induced by obesity in the adipose tissue [10] The proinflammatory cytokines secreted by the inflammed adipocytes disrupt the normal function of adipose tissue itself as well as that of remote organs [11] Adipokines like leptin and adiponectin secreted by adipose tissue, further modulate the inflammation. Leptin, elevated in obesity, enhances inflammation by activating macrophages and T cells, while adiponectin, an anti-inflammatory adipokine, is reduced in obesity. The imbalance between these adipokines in MetS intensifies the inflammatory response [7].

Oxidative Stress:

Besides inflammation, oxidative stress has been implicated in the pathophysiology of Metabolic syndrome [12]. Oxidative stress is a phenomenon caused by an imbalance in overproduction of deleterious reactive oxygen and nitrogen species (ROS and RNS) and the impairment of antioxidant enzymes such as superoxide dismutase (SOD) or glutathione peroxidase (GPx) [13]. Oxidative stress is a key mediator in the development and progression of multiple pathophysiological conditions associated with MetS, such as endothelial dysfunction, hypertension and atherosclerotic cardiovascular disease [14]

Fig.1 Etiopathogenesis of Metabolic Syndrome



Both Genetic and acquired variables play a role in the pathophysiology of Metabolic Syndrome, contributing to the final pathway of inflammation that ultimately leads to cardiovascular disease. The fact that the geographic distribution of Metabolic Syndrome varies greatly and that there has been a recent "catch up" in

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the developing world highlight the significance of lifestyle and environmental variables, such as consumption of extra calories and lack of physical activity being key factors. It has been shown that visceral adiposity is the main initiator of most of the metabolic syndrome pathways, highlighting the significance of a high caloric intake as a major contributing factor. Insulin resistance, neuro-hormonal activation, and chronic inflammation seem to be the primary key players in the onset, development, progression, and transition of Metabolic syndrome to CVD [15]

Chronic inflammation is known to be associated with visceral obesity and insulin resistance which is characterized by the production of abnormal adipocytokines such as tumor necrosis factor α, interleukin-1 (IL-1), IL-6, leptin, and adiponectin. The interaction between components of the clinical phenotype of the syndrome with its biological phenotype (insulin resistance, dyslipidemia, etc.) contributes to the development of a pro-inflammatory state and further a chronic, subclinical vascular inflammation which modulates and results in atherosclerotic process. For such a population, lifestyle modification remains the primary intervention of choice [16]

***Cinnamomum zeylanicum* (Cinnamon) for the Management of Metabolic Syndrome** Cinnamon, the inner bark of a tropical evergreen tree has two main varieties, *Cinnamomum cassia* (*Cinnamomum aromaticum*) and *Cinnamomum zeylanicum* [17] Cinnamon, known as Darchini in Unani medicine is derived from the bark of *Cinnamomum zeylanicum*. It has been widely recognized in Unani medicine for its diverse therapeutic benefits.

In Unani medicine, Darchini is classified as having a warm and dry temperament (*Mizaj*), making it effective in treating various ailments related to digestion, circulation, and the nervous system. It is a widely used herb in Unani medicine due to its carminative, antiseptic, liver tonic, nervine tonic, and astringent properties [18]. Unani scholars such as Ibn Sina and Al-Razi have documented its efficacy in treating ailments related to the gastrointestinal, cardiovascular, and respiratory systems [19,20]

Botanical Description:

Cinnamomum zeylanicum is a small evergreen tree belonging to the Lauraceae family. It is primarily cultivated in Sri Lanka, India, and other tropical regions. [21,22]

Key botanical features include: [21–23]

- *Leaves:* Simple, opposite, and ovate with a glossy green surface.
- *Bark:* Highly aromatic, smooth, and reddish-brown, used as a primary medicinal component.
- *Flowers:* Small, pale yellow, and clustered in panicles.
- *Fruits:* Dark purple drupes containing a single seed.

Phytochemical Composition:

Cinnamomum. zeylanicum contains bioactive compounds that contribute to its medicinal properties, including:

- *Cinnamaldehyde:*

The primary active component with anti-diabetic and anti-inflammatory effects [24] Cinnamaldehyde compound has protective effects on cardiovascular conditions like cardiac ischemia, hypertrophy, and myocardial infarction [25]

- *Eugenol:*
- Eugenol is a bioactive compound available in Cinnamon. The compound is known for its antioxidant, antimicrobial, anesthetic, anti-inflammatory, neuroprotective, anti-diabetic, cardiovascular and anti-cancer activities [26,27]
- *Polyphenols and Flavonoids:*

The polyphenolic content phenolic acids, flavonoids, stilbenes and lignans of *Cinnamomum zeylanicum* in experimental studies, have shown anti-inflammatory and antioxidative properties and improved insulin sensitivity and carbohydrate metabolism. Clinical studies also indicate improvement in anthropometric parameters, inflammatory mediators, glycemic indices and lipid profiles in patients with type-2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease [28].

Coumarins:

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Coumarins, the natural plant compounds with strong anticoagulant properties are present in higher concentration in *Cinnamomum cassia that* can potentially exert toxic effects on the liver. However, *Cinnamomum zeylanicum* used as Darchini in Unani medicine is known for its lower coumarin contents which influence blood circulation and reduce hypertension [17,28]

Pharmacology of *Cinnamomum zeylanicum*:

- *Anti-Diabetic Activity:*[29]
- Enhances insulin sensitivity and glucose uptake by stimulating membrane translocation of GLUT-4.
- Modulates key enzymes in carbohydrate metabolism: In-vitro studies of have demonstrated that *Cinnamomum zeylanicum* has a potential for i) reducing intestinal glucose absorption by inhibiting the activity pancreatic α–amylase and α–glucosidase. *In-vivo* studies have demonstrated that *Cinnamomum zeylanicum* increases circulating insulin levels, reduces fasting blood glucose and HbA1c levels in diabetic patients.

- *Lipid-Lowering Effects:*[29]

Pharmacological studies showed that *Cinnamomum zeylanicum*:

- Decreases total cholesterol, LDL cholesterol, and triglycerides.
- Increases HDL cholesterol, improving lipid profiles.

- *Antihypertensive Properties:*
  - Promotes vasodilation and reduces arterial stiffness: Cinnamon exhibits protective effects against atherosclerosis by inhibiting various pro-atherogenic cellular events like endothelial dysfunction, oxidative stress, platelet activity and thrombosis [30]
  - Lowers systolic and diastolic blood pressure: Several studies have shown that Cinnamon exerts hypotensive effects through various mechanisms, such as improving endothelial dysfunction, regulating ion channels, and suppressing oxidative stress. The production of NO has a protective effect on the endothelium [31]

- *Anti-Inflammatory and Antioxidant Mechanisms:*
  - Ethanol extract of *Cinnamomum zeylanicum* has shown suppression of intracellular release of TNF-α in murine neutrophils as well as leukocytes in pleural fluid. The extract was found to inhibit TNF-α gene expression in LPS-stimulated human peripheral blood mononuclear cells (PBMCs) at 20 μg/mL concentration [32]
  - The bark of *Cinnamomum zeylanicum* has strong antioxidant and free radical scavenging activity [33] The essential oils obtained from the bark of *Cinnamomum zeylanicum* and eugenol has shown very powerful activities decreasing 3-nitrotyrosine formation and inhibiting the peroxynitrite-induced lipid peroxidation in *in-vitro* assays [29]. Oxidative stress and the inflammatory response may lead to islet β cell injury. Attenuating oxidative stress and anti-inflammation are crucial ways for Cinnamon to treat diabetes. *Cinnamomum zeylanicum* protects pancreatic beta cells from oxidative damage due to its antioxidant and free radical scavenging activity [30].

- *Anti-Obesity activity:*
  - *Inhibits adipogenesis and enhances lipid metabolism:*

Polyphenolic compounds with anti-obesogenic effects are abundant in Cinnamon species. *In vitro* studies showed that differentiation of adipocyte could be inhibited by polyphenolic compounds; also they inhibited lipolysis, lipogenesis or intestinal lipid absorption that they tend to lowering weight. Polyphenolic compounds are inducers of fatty acid oxidation or antagonist at cannabinoid receptors and attenuate the inflammatory changes [33]

Mechanisms of Action of *Cinnamomum zeylanicum:*

- *Enhancement of Insulin Signaling:*

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Cinnamon contains bioactive compounds that activate insulin receptors and glucose transporters [34,35]

- *Reduction of Lipogenesis:*

Inhibits enzymes involved in lipid synthesis, thereby reducing hyperlipidaemia [36]

- *Anti-inflammatory Pathways:*

Modulates NF-κB and cytokine pathways to reduce systemic inflammation [37]

- *Antioxidant Protection:*

Neutralizes free radicals and enhances endogenous antioxidant defense mechanisms. [30]

Discussion

Darchini *(Cinnamomum zeylanicum)* presents a multifaceted approach to the treatment and prevention of metabolic syndrome by targeting key physiological pathways associated with the disorder. One of the primary mechanisms through which Cinnamon exerts its benefits is by improving insulin sensitivity, which plays a critical role in controlling blood sugar levels and preventing the progression of type 2 diabetes. The polyphenolic compounds found in Cinnamon, particularly methylhydroxychalcone polymer (MHCP), have been shown to mimic insulin activity and enhance glucose uptake, making it a valuable natural alternative for managing hyperglycaemia.

In addition to its hypoglycemic properties, Darchini contributes significantly to lipid profile improvement. The regulation of cholesterol and triglyceride levels is essential in metabolic syndrome management, as dyslipidemia is a major contributing factor to cardiovascular complications. Clinical studies have demonstrated that Cinnamon supplementation leads to a reduction in total cholesterol, LDL cholesterol, and triglycerides, while simultaneously increasing HDL cholesterol, thus promoting cardiovascular health.

Another critical aspect of metabolic syndrome is chronic low-grade inflammation, which has been identified as a major driver of insulin resistance and cardiovascular disease. The anti-inflammatory and antioxidant properties of Cinnamon help mitigate oxidative stress and reduce pro-inflammatory cytokine levels, thereby protecting vascular health and reducing the risk of endothelial dysfunction.

Furthermore, Cinnamon's ability to regulate blood pressure through vasodilatory mechanisms offers additional protection against hypertension, a key component of metabolic syndrome. By enhancing nitric oxide production and reducing vascular resistance, Cinnamon helps maintain healthy blood circulation and prevents arterial stiffness, which are crucial in reducing the risk of heart disease.

Weight management is another area where Cinnamon shows promising effects. By influencing lipid metabolism, promoting fat oxidation, and modulating appetite-regulating hormones like leptin and ghrelin, Cinnamon can aid in controlling obesity, a major risk factor for metabolic syndrome. Its ability to suppress appetite and enhance satiety may contribute to reduced caloric intake and better weight control.

Taken together, the diverse pharmacological properties of *Cinnamomum zeylanicum* highlight its potential as a natural, adjunctive therapy for metabolic syndrome. However, while the current evidence is promising, further large-scale clinical trials are necessary to establish standardized dosages, long-term safety, and efficacy in diverse populations.

Conclusion

Darchini *(Cinnamomum zeylanicum)* exhibits multiple therapeutic properties that make it a promising natural intervention for metabolic syndrome. Its ability to regulate glucose metabolism, improve lipid profiles, exert anti-inflammatory effects, and support cardiovascular health highlights its potential role in managing metabolic syndrome. Further large-scale clinical trials are needed to establish standardized dosages and confirm long-term safety.

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