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Review Article

Effects of Stevia on Hypertension of Metabolic Syndrome: A Systematic Review

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ABSTRACT

By the importance of dealing with metabolic syndrome (MetS), this work was performed to systematically review available articles on effects of stevia on hypertension as a leading risk factor of metabolic syndrome. The stevia extracts are natural resource of non-caloric sweeteners and they attracted attentions of researchers especially in recent years for dealing with the issues of metabolic syndrome. To this aim, stevia effects on hypertension were reviewed based on the obtained results of original research publications of the following electronic databases: Web of Science, Scopus, and PubMed, from 2010 to June 2022. The following search strategy was used: (stevia OR stevia rebaudiana OR sweet leaf OR stevioside) AND (hypertension OR blood pressure). Six articles were eligible to be included in this review; three *in vivo* studies, one *in vivo*/*in vitro* study, and two clinical trials. Based on the results of *in vivo* studies, positive effects of stevia on lowering blood pressure were found besides observing an enzymatic inhibition activity through the *in vitro* results. The results of one of clinical trials reported a significant reduction in blood pressure after twelve weeks of stevia consumption, but the other one did not report any significant effect. Although the relatively low methodological rigor of these experiments limits the strength of these findings, further clinical trials and regulatory assessments are warranted.

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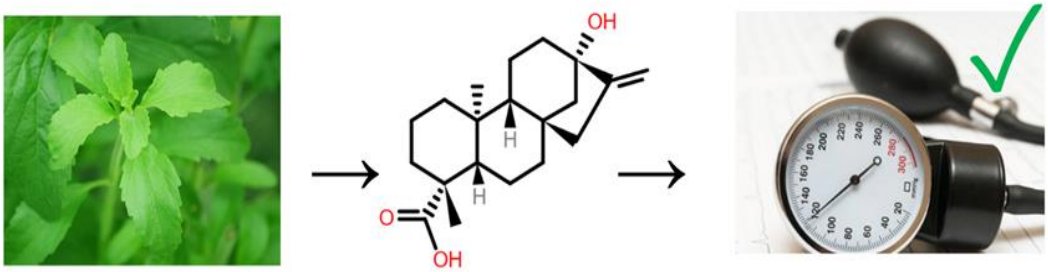
GRAPHICAL ABSTRACT



Introduction

Stevia (*Stevia rebaudiana*) is herbal plant with the major component of stevioside, which is extracted from the leaf and stem tissues of stevia as a sugar substitute [1]. The extracts of stevia were found to be natural sources for non-caloric sweeteners consumptions as alternatives to the synthetic sweetening agents and sugars [2]. The point is that the stevia-based sweeteners do not break through the digestive processes of human body system. Hence, these types of sweeteners are helpfull to control the blood sugar level in diet programs [3]. Besides such typical sweeting functions, many other therapeutic activities have been found for stevia against diseases and disorders such as cancer, inflammation, and hypertension [4-6]. The first use of stevia-based compounds was in food industries, but they are also considered to be therapeutic agents nowadays [7]. Accordingly, several types of investigations in all *in silico*, *in vitro*, *in vivo*, and clinical media have been carried out on stevia to recognize there featured activities [8-11]. Besides such therapeutic importance, a general demand has been arisen on use of stevia as a natural product in everyday life style package [12]. Therefore, the basis of such demand should be investigated to learn various sides of stevia for everyday use [13]. To this time, several investigations have been done to develop the knowledge on stevia and its related compounds [14]. Based on the earlier results, stevia effects on metabolic syndrome have been reported and stevia has been seen as a useful component for preventing or controlling some of diseases and disorders [15]. In this regard, the current review was done to systematically provide some more insights on stevia and its features applications in the metabolic syndrome aspects.

Metabolic syndrome (MetS) is a complex of metabolic disturbances and risk factors of other diseases and disorders such as cardiovascular diseases, type 2 of diabetes, obesity, hyperglycaemia, and hypertension [16-18]. Within recent years, many people have complained for the negative impacts of metabolic syndrome leading to a serious need of developing novel protocols of preventing or controlling such emerging global epidemic [19-21]. Referring to a common definition; glucose intolerance, obesity, dyslipidaemia, and hypertension are essential components of metabolic syndrome with their own details and criteria [22]. Among the mentioned components, hypertension has been remaining as a major challenge to human health systems defined by a chronically increase of blood pressure above 140/90 mmHg [23]. Hypertension has been assumed as a leading risk factor of major health problems affecting ~30% of adults with cardiovascular problems such as heart attack and stroke, chronic kidney disease, heart failure, cognitive impairment, and dementia [24]. As a result, developing new strategies of dealing with hypertension is a must for saving the human health system [25-27]. It is worth to mention that terms of exploring novel medications are very important for the reasons of dealing with several known and unknown diseases, in which several protocols have been always developing to overcome the medical issues [28-30].

Not only for the drug related issues, but also several other biomedical applications have been developed during the recent years [31-33].

Especially in the case of treatments of diseases, the results indicated that the problem is still under development and several other requirements are needed for succeeding in such issue [34-36]. Learning details of materials are very important for customizing them for specific applications, and such issues are currently the targets of several studies using various aspects and methods [37-40]. Among such efforts, the herbs have been found very interesting to be explored in addition to the exploration of other types of drugs and biomaterials modifications [41-43]. To this aim, the current review work was systematically focused on effects of herbal sativa on hypertension to provide more insights into the issues of metabolic syndrome. Due to the complexity of both known and unknown diseases, exploring their features for developing their applications are essential for approaching a more successful treatment for patients and infected persons [44-46].

Materials and Methods

The goal of this review was to systematically evaluate the stevia effects on hypertension to provide insights into metabolic syndrome. The structural representation of steviol as the main building block of stevia besides its known herbal leaf was displayed in Figure 1 [47, 48]. To approach the goal of this systematic review work, the stevia effects on hypertension were reviewed based on the original research publication of the following electronic databases: Web of Science, Scopus, and PubMed, from 2010 to June 2022. The following search strategy was used: (stevia OR stevia rebaudiana OR sweet leaf OR stevioside) AND (hypertension OR blood pressure). The published articles in English language were included in the search results. In the intial step, the articles were screened based on the title and abstracts. Next, the selected relevant articles were reviewed deeper. The titles and abstracts of the selected articles were screened by two reviewers and a third reviewer checked all the results for making a confirmation. To assess the quality of involved articles in this review, methodological parts of articles and their goals and achievements were carefully studied to learn about their suitability for approaching the goal of this work. Because different types of articles were included in this work; *in vitro*, *in vivo*, and clinical trials, a common point of investigating effects of stevia on hypertension was followed through them besides the concepts of titles and abstracts to confirm their eligibility for including in the current review work.

Results and Discussion

Contents of electronic databases of Web of Science, Scopus, and PubMed, based on titles and abstracts were screened and the results indicated the existence of six original research articles after assessing the inclusion/exclusion criteria [49-54]. The characteristic features of the screened articles were summarized in Table 1. All selected articles evaluated the stevia effects on hypertension in different media. Accordingly, their features were categorized into *in vitro*, *in vivo*, and clinical studies, and also, they were prepared for discussion.

As mentioned earlier, hypertension is assumed as a leading risk factor of several other serious diseases and disorders in the category of metabolic syndrome [23]. Accordingly, exploring efficient protocols of treatment of hypertension is a must [25-27]. To this aim, earlier works indicated benefits of consumption of natural products for preventing or controlling hypertension or blood pressure in human health systems. Among them, the typical herbal plant stevia has been seen useful for several purposes as a food additive or a therapeutic agent. Stevia and its components have been vastly investigated during the recent years to learn their features and applications. In this regard, the current review work was done to systematically explore the available studies on the issue of effects of stevia on hypertension to provide an answer to a question on further employing of stevia and its developments. Hence, the available works on all three methodological approaches of *in vitro*, *in vivo*, and clinical trial, were systematically investigated to include both of its scientific developments and medical treatments.

Table 1: Characteristic features of included articles

First author	Year	Type of study	Name of Component	Detail of methods	Outcome	Comments
Vílchez et al., [49]	2022	*In vivo*	Extract of stevia rebaudiana and Uncaria tomentosa (GlucoMedix ®)	In hyperglycemic (alloxan-induced and glibenclamide-controlled), hyperlipidemic (cholesterol-induced and atorvastatin-controlled), and hypertensive (L-NAME-induced and enalapril-controlled) rat models assessment of Acute toxicity and 28-day subacute toxicity.	Daily oral doses of 250 - 1000 mg/kg reduces hyperglycemia, hyperlipidemia, and hypertension in rat models without toxicity.	Treats all three comorbidities.
Bhatt et al., [50]	2020	*In vivo*	Pure sativoside	Standard cardiotoxicity models—isoproterenol-induced myocardial infarction and Ischemia-Reperfusion Injury (IRI) through modified Langendorff setup was used to test this hypothesis. Rats were randomly divided into control groups (normal—physiological saline and toxic—isoproterenol, 150 mg/kg, s.c., and IRI induced in normal control animals) and treatment groups (diltiazem—17.5 mg/kg, p.o., stevioside—100 and 200 mg/kg, p.o. and combination groups). At the end of the treatment period, animals were sacrificed and biochemical, electrocardiographic, and histopathological changes were measured.	sativoside showed protective action on levels of tissue antioxidant enzymes (SOD and Catalase), electrocardiographic parameters (HR, RR, QRS, QT, PR), and heart tissue histopathology when compared to concurrent toxic control groups. Combination of stevioside (200 mg/kg) and diltiazem (17.5 mg/kg) exerted a more significant pharmacodynamics response.	Conclusion: Stevioside and diltiazem both displayed radioprotective effect when given alone. Co-administration displayed improved restorative action on antioxidant status, biomarkers, electrocardiographic parameters, and histology.

García-Arroyo et al., [51]	2016	*In vivo*	water sweetened with the non-caloric edulcorant stevia	Recurrent dehydration was induced in rats by exposure to heat (36 °C) for 1 h / 24 h followed by access of water (W), a 11% fructoseglucose solution (FG, same composition as typical soft drinks), or water sweetened with non-caloric stevia (ST). After 4 week plasma and urine samples were collected, and kidneys were examined for oxidative stress, inflammation, and injury.	Rehydration with stevia water did not produce kidney injury, stevia rehydration was associated with lower blood pressure than the group rehydrated with water.	Stevia-rehydrated animals had normal blood pressure and no evidence of renal tubule damage.
Wang et al., [52]	2019	*In vitro/ in vivo*	Ethanol extract of stevia leaves, steviol glycosides and protein hydrolysates	Inhibition of Angiotensin-converting enzyme activity/ hypertensive rats were randomly divided into four groups: control (Purina Rat Chow + water), test group 1 (Purina Rat Chow + the formulated solid drink), test group 2 (Purina Rat Chow + the coffee drink) and test group 3 (Purina Rat Chow + the tea drink). Each group had 10 animals.	The ethanol extract of stevia leaves, steviol glycosides (with 95% purity; natural sweeteners widely used in the food industry) isolated from the ethanol extract and stevia leaf protein hydrolysates inhibited 26.60%, 59.56% and 74.38% of angiotensin-converting enzyme activities, respectively animal test showed that they had a significantly antihypertensive effect in spontaneously hypertensive rats.	
Stamataki et al., [53]	2020	Randomized, controlled, open-label 2-parallel arm trial	Commercially available stevia drops product (SweetLeaf ®)	Healthy adults were randomized to the 2 study groups and consume 5 drops twice daily with their habitual drinks for 12 weeks. Effects of daily stevia consumption on Glycaemia, Body	There was a significant main effect of group on BW change [F(1,26) = 5.56, p = 0.026)] control group). The energy intake was significantly	

				Weight (BW) and Energy Intake (EI) and Blood Pressure.	decreased between week 0 and 12 in the stevia group (p = 0.003, no other significant changes were observed for waist circumference, systolic and diastolic blood pressure, or pulse rate.	
Rizwan et al., [54]	2019	Randomized, single-blind, placebo-controlled trial	Stevioside capsules	Stevia capsule (250 mg) or matching placebo was given to the chronic kidney disease (CKD) patients twice daily along with Angiotensin-II Receptor Blocker (ARB) and/or Ca Channel Blocker (CCB) for 3 months.	Significant changes were found in Diastolic Blood Pressure (p<0.001), Systolic Blood Pressure (p<0.000), Serum Creatinine (p<0.027), Serum Uric Acid (p<0.009), Fasting Blood Sugar (p<0.041) and Postprandial Blood Sugar (p<0.013) and Micro Albumin (p<0.041) level in the treatment.	But the current study indicated that both the Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) significantly reduced in stevia and placebo group in human subjects.

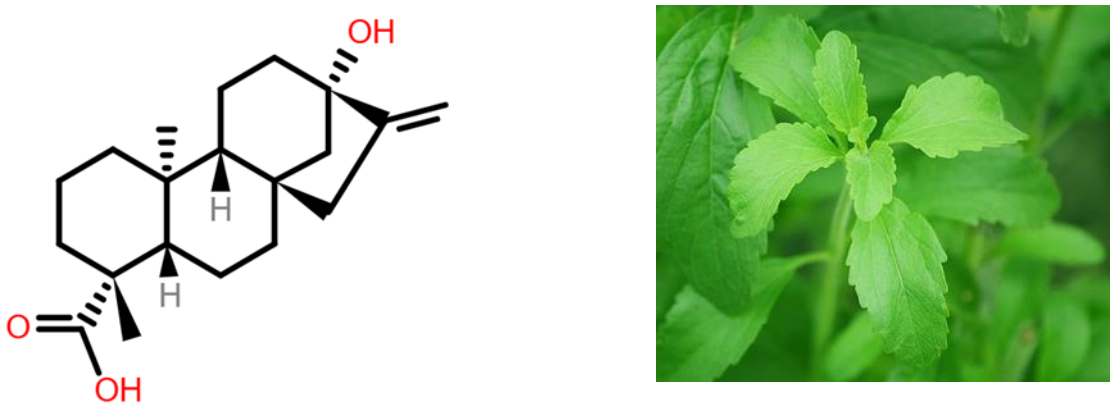


Figure 1: The structural representation of steviol and a known herbal leaf of stevia [47, 48].

GlucoMedix® has been very recently reported as an extract of stevia for dealing with the metabolic syndrome [49]. Within the reported *in vivo* work, hyperglycemic, hyperlipidemic, and hypertensive symptoms were investigated in the rat models under assessing acute toxicity and a 28-day subacute toxicity. The results indicated that daily oral doses of 250-1000 mg/kg could reduce all symptoms of hyperglycemia, hyperlipidemia, and hypertension in rat models without any significant toxicity. Accordingly, consumption of stevia-based GlucoMedix® has been seen useful for controlling the hypertensive symptoms. In another *in vivo* study, pure stevioside was administrated in combination with diltiazem, in which the results indicated benefits of such combined treatments in rat models to control the hypertensive symptoms [50]. Indeed, an anti-oxidant feature of stevioside was the conducting agent of such more efficient observation. The kidneys of rat models were examined under dehydration/rehydration processes and the

results indicated that those rehydrated rats with stevia-sweetened water showed a lower blood pressure than rehydrated rats with the pure water [51]. As a consequence, the results of *in vivo* studies showed benefits of stevia treatments on lowering or controlling the blood pressure level and hypertensive symptoms [52-54].

In a combined *in vitro*/*in vivo* study, an enzyme inhibitory activity and an antihypertensive effect were observed for a stevia based extract; steviol glycosides [52]. The results indicated significant effects of steviol glycosides on the inhibition of angiotensin-converting enzyme (ACE) activity. Moreover, the rat modes showed significant impacts of steviol glycosides administration for lowering the spontaneously hypertensive symptoms. As a consequence, an enzymatic activity inhibition was shown in this work for learning the basis of antihypertensive function of the stevia-based extract through performing an *in vitro*/*in vivo* study.

Besides such typical achievements about effects of stevia on hypertension through *in vivo* and *in vitro* media, two works were reported trial analysis for examining such effects in the human system [53, 54]. Their results indicated effects of stevia-based components on hypertension in terms of lowering blood pressure or not to changing its level after the consumption of stevia. Accordingly, a significant role of stevia was seen for the human system for dealing with hypertensive symptoms.

Limitations and strengths

It is very important to mention that the topic of human health related developments is very crucial for maintaining the quality of life system [55-58]. The existence of several wild diseases in both of already available or newly born cases causes serious issues to human health system and treatments are not still certain [59-62]. In this regard, several limitations are remaining for investigating new topics of human health related systems and several further investigations are still required for approaching a success in this case [63-67]. The initiation of physiological problems is somehow related to several other diseases and disorders in the human body and it could also initiate other diseases and disorders [68-70]. In this case, the current work was done to provide more insights on targeted topic of hypertension and developing a possible herb-based treatment. The major limitation and again strength of this work was to inclusion all three methodological works; *in vitro*, *in vivo*, and clinical trial, in the current review to systematically provide scientific insights and features applications for stevia on the issue of hypertension. The limitation of this work was to see how to converge the achievements of different methods and the strength of this work was to include all available achievements to make a clear insight into the topic of this work. As a consequence, the major limitation of the work was almost the major strength of the current work for the available articles. However, few studies were done on the issue of effects of stevia on hypertension, especially in clinical trials, in which this is a limiting factor for making more highlighted conclusions on the significance of stevia effects on hypertension.

Conclusion

By approaching the goal of this work to show effects of stevia on hypertension as a leading risk factor of metabolic syndrome, available articles regarding *in vitro*, *in vivo*, and clinical trials were reviewed to provide a systematic insight on the investigated issue. Based on the results of *in vivo* studies, benefits of stevia treatments on lowering or controlling blood pressure level and hypertensive symptoms were observed. In addition, an enzymatic activity inhibition was shown in a combined *in vitro*/*in vivo* study with the results of antihypertensive functions of the stevia-based extract. By the results of clinical trials, a significant role of stevia was seen for the human system to deal with the hypertensive symptoms. However, more clinical trials with long-term follow-up studies are still needed to investigate the significance of stevia effects on the hypertension towards controlling the metabolic syndrome issues.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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