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Hibiscus Miracle in Treatment of Hypertension

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ABSTRACT

Hypertension is a global health problem with significant magnitude of morbidity and mortality, in recent years, most of the developing countries such as Sudan depend largely on the herbal remedies which are used for the treatment of hypertension such as: *Hibiscus Sabdariffa*. In folk medicine it is used for variety aspects such as: wound dressing, bronchitis and diabetes. The extract of this plant exerts its antihypertensive activity by at least three major specific mechanisms of action: diuretic, vasodilator and angiotensin converting enzyme inhibitor (ACE inhibitor)**.**The object of the work was to to discuss and evaluate the effectiveness of *Hibiscus Sabdariffa* as antihypertensive agent. In vitro, *H. sabdariffa* (HS) act as a vasodilator via relaxed the pre-contracted endothelium-intact and endothelium-denuded aortic rings. In man and laboratory animals, aqueous extraction of HS significantly reduced BP in essential hypertensive man, and the calyx extract reduced BP in the spontaneously hypertensive rat. It's also significantly reduced BP in normal rats and anesthetized cats. In addition, there are an evidence reports that the regular use of (HS) can protected the body from the cardiovascular disorder by lowering: total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides in the majority of normolipidemic, hyperlipidemic and diabetic animal models. All the studies had agreed that *Hibiscus Sabdariffa* can significantly reduce the blood pressure, but all the problems that reported later on in the discussion that have founded on the conducted articles need further evaluation of this herbal remedy to be approved as an effective antihypertensive agent.

Keywords: Hypertension, *Hibiscus Sabdariffa*, Hyperlipidemic and diabetic animal models

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INTRODUCTION

Hypertension is a major metabolic syndrome that is characterized by abnormally high arterial blood pressure that is usually indicated by an adult systolic blood pressure of 140 mm Hg or greater or a diastolic blood pressure of 90 mm Hg or greater according to Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)[1], it is chiefly of unknown cause but may be attributable to a preexisting condition (as a renal or endocrine disorder)

This condition is a global health problem with significant magnitude of morbidity and mortality, it has been estimated that 1 billion individuals all over the world suffer from hypertension causing up to 7.1 million deaths per year, which is about 13% of total death worldwide, [3] it is a major risk factor for cardiovascular disease estimated to account for 35% of myocardial infarction and stroke, 49% of heart failure, and 24% of premature mortality .

Lifestyle modification, including dietary change, exercise and weight reduction is the recommended first-line approach to prehypertension[4] although drug treatment is often necessary in people for whom non pharmacological treatment is prove ineffective or insufficient. Many groups of drugs could be used effectively for treatment such as diuretics , rennin – angiotensin system blocker , beta blocker , calcium channel blocker , alpha blocker , centrally acting adrenergic blocker and direct vasodilators but they are costly, uncomfortable and can produce some undesirable side effects.

Studies revealed that about 80% of people in developing countries[5] still relays on traditional medicine based largely on species of plants and animals for their primary health care and these alternative treatment currently in demand and it is popularity increasing day by day because it's affordable, comfortable and Accessible to everyone such as: Zingiberaceae (*Zingiber officinale*), Ginkgoaceae (*Ginkgo biloba*) and Malvaceae (*Hibiscus Sabdariffa*). [6]

Hibiscus is a genus of flowering plants in the mallow family, Malvaceae. It is quite large, containing several hundred species that are native to warm-temperate, subtropical and tropical regions throughout the world such as *Hibiscus acetosella* known as False Roselle, *Hibiscus aculeatus* known as Comfortroot, *Hibiscus biseptus* known as Arizona Rosemallow and *Hibiscus Sabdariffa* Linne the head title of this review paper[7].

Hibiscus Sabdariffa Linne, known as Roselle or Red Sorrel in English-speaking countries .It is a tropical plant widely grown in Central and West Africa, South-East Asia and elsewhere. Common names besides Roselle are Red Sorrel, Karkade, sour tea and red tea. Various parts of Roselle (

flower ,leaves ,calyx and corolla) are used as beverages in China, Taiwan and Thailand both as a thirst-quenching drink [5].

In folk medicine *Hibiscus Sabdariffa* Linne HS used for wound dressing, bronchitis, diabetes, [8]cardiac and neurologic diseases, repair of calcified vessel, antispasmodic, hypochlosterolemic , antibacterial , antifungal ,anticancer, muscle relaxant effects[9] and recently as antihypertensive agent.

The extract of this plant exerts the antihypertensive activity by at least three major specific mechanisms of action: diuretic[10], vasodilator[11] and angiotensin converting enzyme inhibitor (ACE inhibitor)[12] but there are additional mechanisms of action hibiscus exert can reduce high blood pressure on long term use as antioxidant[13] and hypocholesrolemic[14] which considered as a cardio protective effect.

HS act as diuretic by inhibition of sodium (Na^+) and water re-absorption it has an advantage over the loop diuretic furosemide that it does not cause over-reactivation of the rennin-angiotensin-aldosteron system and maintaining the potassium concentration in the body this was evidenced by the potassium K^+ values, corresponding index and the saluretic relationship of Na^+/K^{+15}.

ACE inhibitor effect exert by HS due to the blockage of the angiotensin 1 receptor binding to angiotensin II therefore, angiotensin II is not produced and aldosterone is not released from the adrenal gland, which may eventually cause a decrease in the vascular resistance[9]..

In vitro, *H. sabdariffa* (HS) act as a vasodilator via relaxes pre-contracted endothelium-intact and endothelium-denuded aortic rings. The hypotensive effect of HS does not appear to be mediated via inhibition of sympathetic nervous system, but may be mediated via nitric oxide (NO) or partly via inhibition of calcium Ca^{2+} influx through receptor-gated channels[16] .

In vivo, administration of HS caused a reduction in blood pressure (BP). Thus, aqueous extraction of HS significantly reduced BP in essential hypertensive man and the calyx extract reduced BP in the spontaneously hypertensive rat. HS also significantly reduced BP in normal rats and anesthetized cats.[17]

in addition, there is an evidence report that the regular use of HS can protect from the cardiovascular disorder by lowering Total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides in the majority of normolipidemic, hyperlipidemic, and diabetic animal models[18] .

Regarding this situation in Sudan, traditional medicine together with use of medicinal plants represent an important part of the cultural heritage, because the Sudan has witnessed the fusion of

many cultures, Pharonic, Christian and Islamic along with the local indigenous cultures and vast variety of climate conditions [19].

Sudan considered as the country in which Roselle originated particularly in Kordofan and Darfur areas, and have been domesticated in western Sudan before 4000 BC[19] .

Locally it's called "karkade", the dry calyx is used to produce a flavorsome and healthy drink. The dried calyces are used for tea, jelly, marmalade, ices, ice cream, sorbets, butter, pies, sauces, tarts, and other desserts. The seeds have also been used as an aphrodisiac coffee substitute[19].

It's also have certain therapeutic properties; the reported benefits of taking it internally in the form of herbal tea include: soothing colds, clearing a blocked nose, clearing mucous, as an astringent, promoting kidney function, aiding digestion, general tonic, diuretic and reducing fever . Taken as a calyx drink, it is a mild diuretic and purgative, among many other effects. The drink is said to be a folk remedy for cancer[19] and the hot delicious drink of hibiscus is strong complementary medicine for treatment of hypertension .

Lowering blood pressure level will likely decrease the risk of stroke and cardiovascular disease. Therefore, evaluating the antihypertensive effect of HS will open doors for researchers to devote effort, time and money on this herbal remedy to be one of the 1st line therapies for hypertension and even cancer in future.

MATERIALS AND METHOD

Criteria for considering studies for this review:

According to type of studies : All randomised controlled trials (RCT) comparing the use of any forms of Roselle with placebo , to other herbal or pharmacological preparation (or no intervention) in patients with hypertension. According to type of participants : Adults (18 years or older) who had at least 140mmHg systolic blood pressure or at least 90 mmHg diastolic blood pressure. At least two BP measurements were needed at baseline to qualify patients as being hypertensive. Pregnant women were excluded

Search methods for identification of studies:

The Database of Abstracts of Reviews of Effectiveness (DARE) and the Cochrane Database of Systematic Reviews were searched for related reviews. The following electronic data bases were searched for primary studies from 1997 to 2013:

1. The Cochrane Central Register of Controlled Trials (CENTRAL)
2. English language databases, including MEDLINE , pubmed , hinari , google scholar , science direct

3. ClinicalTrials.gov

Using the search words (Hibiscus, Hibiscus Sabdariffa, Sour tea, Roselle , Red sorrel , Karkade , Jamaica , Florde Jamaica , herbal tea , herbal medicine) and in combination with (high blood pressure , elevated blood pressure , hypertension ,pre-hypertension , mild hypertension) .

RESULTS AND DISCUSSION

All reports agreed that Hibiscus Sabdariffa has antihypertensive, antioxidant and hypocholestrolemic effect.

Antihypertensive effect:

(Mckay et al) found that in randomized clinical trial when serving 3 of 240 ml/day of hibiscus tea had a significant change in the mean arterial pressure (P = *0.054)* among prehypertensive and mildly hypertensive patients [4] . In vivo experiment (Odigie et al) supports the public belief that the HS may be a useful antihypertensive and cardioprotective agent. They found that the chronic administration of aqueous extract of *Hibiscus Sabdariffa* 250/mg/kg/day can attenuated hypertension and reversed cardiac hypertrophy. In addition to that there was a significant reduction in: systolic BP (P<0.001), heart rate (*P*<0.001) and in the heart weight (*P*<0.05) [17].

Also (Mojiminiyi et al) reported that in vivo experiment when the aqueous extract of the HS calyxes given at doses started from 1-125 mg/kg, the blood pressure and heart rate fell significantly ($P < 0.05$) and this fell was dose dependent[20] .

Moreover, HS is a very useful antihypertensive treatment in diabetic patients as in randomized controlled trial conducted by (Khosravi et al). The continuous consuming of hibiscus tea was significantly decrease the blood pressure (*P* value <0.001) among the diabetic patient.[21]

There is one study in sudan done by under graduated student showed that hibiscus is promised alternative medicine as antihypertensive agent, he showed that the methanolic extract of hibiscus contain 35mg as effervescent tablet formulation can act as antihypertensive agent (design, formulation and quality control of H. sabdariffa extract as effervescent tablets presented by Abde alhakam 2010, Omdurman Islamic university).

Hibiscus can act as antihypertensive agent by different mechanisms, the major mechanisms of action are: diuretics, angiotensin converting enzyme inhibitor and vasodilator

Diuretic mechanism:

(Arellano et al) confirmed the antihypertensive capability of the aqueous extract of the *H. sabdariffa* by studying the effectiveness and tolerability of decoction of dry calyx of HS contained about 9.62 mg/kg of anthocyanin / dose once daily before breakfast and the modification of the

urinary electrolyte induced by this plant compared with captopril, 25 mg twice/day for 4 weeks in a randomized clinical trial.

In this experiment HS showed a significant increment of urinary excretion of sodium ($p<0.001$), without substantially modifying other urinary electrolytes including potassium in which HS exert similar behavior found with the administration of the spironolactone type or aldosterone antagonists which they are potassium sparing diuretics . Also potassium acetate contained in the water extract of the decoction has a moderate diuretic effect could contribute to the antihypertensive effect [22]. This study confirmed the reports that the aqueous extract of this plant exert it's antihypertensive properties as diuretic as in (Alonso et al) study demonstrated the pharmacological characterization of the diuretic and natriuretic effect of *Hibiscus Sabdariffa* aqueous extract (HsAq) in rats with high doses and compared it with the furosemide (loop diuretic) and amiloride (potassium sparing diuretic)[15].

They reported that the diuretic drug furosemide administered at 13 mg/kg, caused urine excretion of 4.8 ml/h. On the other hand, the *Hibiscus Sabdariffa* aqueous extract at doses of 1500, 2000 and 2500 mg/kg induced urine excretion of 3.0, 4.3, 4.4 ml/h of urine, respectively. This effect was significantly different ($p < 0.05$) from the basal volume (1.0 ± 0.5 ml/h) and was evidently dose-dependent. Also urinary excretion of electrolytes after treatment with HsAq revealed a different pattern for each ion (sodium, potassium and chloride). Sodium excretion increased significantly with rising doses ($p < 0.05$), in case of the potassium electrolyte urinary excretion levels showed no differences with different doses of *Hibiscus Sabdariffa* aqueous extract in addition HsAq induced an increment in the urinary Chloride excretion levels in the high doses [15] . This study showed that hibiscus act as diuretic same as furosemide but it have an advantage over furosemide that it maintain the potassium level same without causing hypokalemia as furosemide do.

(Ferrer et al) also confirmed that *Hibiscus Sabdariffa Linn*. Has diuretic, natriuretic, and potassium sparing effects. this study conducted on adrenalectomized rats and the diuretic effect of the plant was measured in the presence of deoxycorticosterone acetate (aldosterone analog)[10]. Aldesterone is steroid hormone produces from the adrenal gland caused conservation of sodium, excretion of potassium and increased water retension therefore increasing blood pressure. The authors conclusion stated that the diuretic, natriuretic, and potassium sparing effects of *Hibiscus Sabdariffa* are due in part to the modulation of aldosterone activity by the presence of compounds in the plant that are potentially responsible for this modulation, as anthocyanins and chlorogenic acid. The dose was not identified in this experiment[10] .

(Aguwa et al) verified The folkloric diuretic activity of the petal methanolic extract of *Hibiscus Sabdariffa linn.* By conducted metabolic assay using graded doses (5 mg/kg – 160 mg/kg) in albino rats as experimental group and compared it with frusemide 3 mg/kg, mannitol 200 mg/kg, hydrochlorothiazide 10 mg/kg, and spironolactone 3 mg/kg in the control group. The urine produced over a period of six hours was collected per animal and its volume, density, pH, and electrolyte concentrations (sodium, potassium, and chloride) were determined. Using standard techniques, the study showed that the extract was found to cause a dose-dependent increase in urine mobilization, which peaked at a dose of 40 mg/kg. At this dose level, the extract showed a significant ($p<0.05$) aquaretic action characterized by a 300-fold increase in urine production, a slight fell in density and urine pH, relative to the control group. Although the extract did not increased the mobilization of the urinary electrolytes assayed, as did the standard diuretics.[23]

Even (KARUM E et al) confirmed that there was a diuretic Effect of the Aqueous Extract of the Calyx of *Hibiscus Sabdariffa* Roselle. His study conducted on the salt loaded rats given a dose of 0.15mg/100 g treatment with the plant extract caused significantly lower ($P<0.05$) serum levels of sodium, bicarbonate, creatinine and urea, while serum potassium was significantly increased ($P<0.05$). he finally concluded that this plant has a nephroprtotective propriety[8].

Angiotensin converting enzyme inhibitor mechanism:

(Arellano et al) experiment concluded that the patients treated with the *H. sabdariffa* extracts showed a significant reduction of the diastolic blood pressure by 12.31 % ($p<0.03$), also The antihypertensive effect observed in both treatment groups (the control and the experiment groups) demonstrated by a decrease of Diastolic blood pressure, Systolic blood pressure, and pulse pressure, as well as the rates of therapeutic effectiveness, was of the same rank with the captopril . In addition there are no significant differences between the aqueous extract from *H. sabdariffa* (standardized on 9.62 mg of total anthocyanins/dose/day) and captopril (25 mg every 12 h.)[22].

Moreover (Jonadet et al) confirmed that the crude hydroalcoholic extract from *Hibiscus Sabdariffa L*. calyces showed appreciable enzyme-inhibiting activity towards the Angiotensin I Converting Enzyme (ACE) in vitro, they concluded that this effect was attributable to anthocyanin.[24]

Vasodilator and antioxidant effect:

(Sarr et al) they studied the vasorelaxation effect of the hibiscus in different methods of extraction: butanolic extract, crude extract, residual marc and ethyl acetate extract. This study was conducted in vivo experiment; the results stated that the *Hibiscus Sabdariffa* crude extract have the greatest ability to activate nitric oxide synthase enzyme and the nitric oxide pathway in the presence of

endothelium. In addition, it have a weak vasorelaxation effect without the presence of endothelium so this led to the suggestion that the crude extract of hibiscus have both endothelium-dependent and independent mechanisms. However, the endothelium-dependent mechanism was much more significant (Emax: 66, 57% ± 8, 07). Another vasorelaxation mechanism induced by anthocyanin is Potassium channels activation, the authors reported that the relaxations obtained with the crude extract in vessels without endothelium, even if they are significantly lower compared with those observed in vessels with intact endothelium, this led to thought that there is a direct relaxing effect of this extract on vascular muscles, The likely mechanism was hyperpolarization of the membrane after direct activation of potassium channels[11.]

Finally, they concluded that the butanolic extraction have the biggest fraction of anthocyanin and the greatest vasorelaxant capacity[11].

(Adegunloye et al) founded that the *Hibiscus Sabdariffa* caused a dose-dependent decreased in the mean arterial pressure (MAP) of the rats. So the final conclusion was the antihypertensive effect of 20 mg /kg extracts of calyx of HS conducted in vivo is not mediated through inhibition of the sympathetic nervous system but it could be mediated through acetylcholine-like and histamine-like mechanisms as well as via direct vaso-relaxant effects[25] .

(Ajay et al) confirmed that the methanolic extraction of hibiscus (0.3 mg/ml) have a concentration dependant vasodilator effect in the isolated aortic rings of hypertensive rats. This probably mediated through the endothelium-derived nitric oxide-cGMP-relaxant pathway and the inhibition of calcium (Ca^{2+})-influx into vascular smooth muscle cells [26].

(obiefuna et al) studied the aqueous extract of *Hibiscus Sabdariffa* petals in vivo and vitro experiments at doses range from (0.02-7.68 mg/ml),they founded that Hibiscus did not show a measurable contractile effect on the vivo experiment but in the vitro experiment a significant vasorelaxation ($p<0.05$) was observed with cumulative concentrations of the Hibiscus and reached a mean of 91 ± 4% at a concentration of 1.70 mg/ml[27] . The improvement of the endothelium relaxation have been related also to the antioxidant capability of the anthocyanin and ascorbic acid in hibiscus as in (Tseng et al)[28] and (Tsai et al)[29] reports, in this vivo experiments the ethanolic extract of the hibiscus dried flowers at concentration of 0.20 mg/ml have a capacity of scavenging free radicals [28]. In addition ascorbic acid found to have the capability of reducing blood pressure by endotheilium dependant or independent vasorelaxation as in the vivo experiment conducted by (Akpaffiong and Taylor).[16]

In addition, (Salah, Gathumbi and Vierling et al) concluded in his vivo experiment that quercetin and eugenol chemical constituents of the *hibiscus* can modulate the Calcium channel and can exerted activity similar to nifidipine [30] .

Hypocholestrolemic effect (indirect antihypertensive effect) :

Many reports suggest that the long term use of Hibiscus can inhibits serum lipids as antiatherosclerotic activity. In (El-Saadany et al) report, after the administration of hibiscus at 5 and 10 % a significant decrease in the activity of the serum alanine transaminase, serum aspratate tranaminase, alkaline, acid phosphatase and total serum protein were detected. The combination of all these significant reduction is an important cardioprotective effect of hibiscus [31] and this will impedes the atherosclerosis formation in the vessel which confirmed by (chen et al) report. they conducted vivo experiment to evaluated the hypolipidemic and anti-atherosclerotic effects of hibiscus, the final conclusion, the levels of triglyceride, cholesterol, and low-density lipoprotein cholesterol (LDL-C) were lowered at 0.5 or 1% and the histopathological examination showed that Hibiscus reduced foam cell formation, inhibited smooth muscle cell migration and calcification of the blood vessels [32].

In (Gurrola-diaz et al) randomized clinical trials suggested the use of Hibiscus in individuals with dyslipidemia associated with Metabolic syndrome. They concluded that the administration of 100 mg / day of hibiscus powder have significantly reduced glucose, total cholesterol levels, increased high density lipoprotein and improved Triglyceride / high density lipoprotein cholesterol ratio. Additionally, a triglyceride-lowering effect was also observed with ($p<0.02$) [33].

In addition (lin et al) concluded that the dosage of 2 capsules of Hibiscus each day with a meal for 1 month can significantly lower the serum cholesterol level. So they suggested that Hibiscus may be effective in hypercholesterolemic patients[14]. On the other hand the antioxdative ability of hibiscus can inhibited also the Low density lipoprotein oxidation and this led to reduce cholesterol degradation as in (chen et al) vivo experiment [13].

Safety and toxicity:

Some studies carried out in animals and humans conducted in this review have primarily demonstrated that there was no change or decrease in measures related to the function of the liver (Aspartate transaminase and Alanine transaminase enzymes) as in (Gurrola-Diaz et al) [33] or in the kidney creatinine enzyme as in (Mohagheghi et al)[34], (Odigie et al)[17] and (Lee et al)[35].

However few studies among animals suggest that Hibiscus extracts had a low degree of acute toxicity ranging from 2000 to over 5000 mg/kg as in (Onyenekwe et al) they found that the calyx infusion lower hypertension significantly (p=0.05) but the plant LD_{50} was above 5000

mg/kg/day[36]. On the hand, (Fakeye et al) concluded that the toxic effect started at dose 2000 mg /kg/day [37]. In contrast, one experiment showed that doses higher as 4600 mg/kg can be administered for several months in an animal model with no report of toxicity although negative effects on testes and sperm count were found as in (Orisakwe, Husaini and Afonne et al) study[38].

There are different points according to these results need discussion. First, is that there are several different species of hibiscus found in different plants[7] but to limit the misunderstanding which species this review is talking about is *Hibiscus Sabdariffa (Karkade) that is used as beverage in Sudan*[19].

All the studies interpreting in this review had agreed that hibiscus had antihypertensive effect but each author concluded that there is a different mechanism of action that hibiscus exert this may be due to the different objectives of how hibiscus exert it's antihypertensive properties in each study such as in [10], [39], and[15] studies.

Second point is the different methods of extraction, during searching the literature each study conducted different method of extraction and according to that there is no agreement from the authors which dose will give the exactly optimum antihypertensive effect. Some authors conducted in their experiment two different method of extraction (butanolic extraction and crude extraction) due to that there was two different doses and a wide range differences in the strength of the main antihypertensive component such as in [11] study. On the other hand some authors conducted only one method of extraction either butanolic extraction , methanolic extraction or aqueous extraction and again each method had a different dose such as in [4],[33],[21].

All the authors agreed that the main component anthocyanin that found in the *Hibiscus Sabdariffa* is the one responsible for the hibiscus antihypertensive effect[27],[28],[29]. On the other hand some authors concluded beside the anthocyanin other component in the hibiscus exert antioxidant properties such as ascorbic acid that inhibit the lipoprotein oxidation that will protect the heart on long term use from elevated blood pressure[29],[16] but further investigation about this effect need to be conduct.

Third point the capability to answer this question, is the antihypertensive effect of the hibiscus appears on the long term use or on short term use? In another word, is the antihypertensive effect of the hibiscus appears at the first dose or after a multiple doses? in the literature some studies have agreed that the Hibiscus Sabdariffa exerted his antihypertensive properties after regular consuming of this plant for one month [22], [17],[9] .

there are many problems found when searching the literature such as : some studies did not show for how long of time the hibiscus have been ingested to excert antihypertensive properties such as

in [10],[3]. one study did not show how the randomized trial was done[9] ,another study show imbalance between the experimental and the control groups on the level of systolic blood pressure and diastolic blood pressure[22] , even withdrawals from the experiments was a big problem found in many studies such as in [22] and [9] studies . Another reporting problem was the lack of attention in the included studies to adverse events associated with the use of hibiscus. So further investigation about adverse events of hibiscus must be conduct.

In addition there are no studies showed which better and fast for hypertension, to drink hibiscus as a hot tea or as a cold juice? So focusing on this question is an important point of view needs further investigation.

Final point is the safety and toxicity of the Hibiscus Sabdariffa most of the studies agreed that the hibiscus had a degree of toxicity at very high doses ingested per day ranging from 2000-5000 mg/kg as mentioned previously .so more randomized clinical trial need to be conduct to confirm the particular toxic dose of the hibiscus.

Table 1: showing the different mechanism of action and doses of *Hibiscus Sabdariffa:*

Author, year	Type of experiment	Type of extraction and Dose of hibiscus	Mechanism of action	Findings
Mckay et al, 2010[4]	RCTs in prehypertensive and mildly hypertensive patients	Aqueous extraction 3 of 240ml/day serving tea	Not identified in the study	Change in the mean arterial pressure (P=0.054)
Odigie et al,2003[17]	Vivo	Aqueous extraction 250 mg/kg/day	Not identified in the study	Significant reduction in: Systolic BP(P<0.001), heart rate(P<0.001) and heart weight(P<0.05)
Mojiminiyi et al,2007[20]	vivo	Aqueous extraction 1-125 mg/kg	Not identified in the study	Significant reduction in blood pressure and heart rate(P<0.05) and this effective was dose dependant
Khosravi et al, 2009[21]	RCTs in diabetic patients	Aqueous extraction Sour tea dose is not identified in this study	Not identified in the study	Significant reduction in blood pressure (P<0.001)
Arellano et al,2004[22]	RCTs in pre-hypertension and stage 1	Aqueous extraction Dose 9.62mg/kg	As diuretic and ACEI	Significant increment of urinary excretion (P<0.001) , significant reduction in diastolic blood pressure (p<0.03)
Alonso et al, 2012[15]	Vivo	Aqueous extraction 1500,2000,2500 mg/kg	As diuretic	Significant urinary excretion of 3.0 , 4.3 , 4.4 ml /hr (P<0.05) respectively*
Ferrar et al , 2012[10]	vivo	Aqueous extraction Dose was not identified in the study	As diuretic	Anthocyanin and chlorogenic acid chmical component of hibiscus responsible for the diuretic activity
Aguwa et al, 2005[23]	vivo	Methanolic extraction Dose (5mg/kg-160mg/kg)	As diuretic	Significant (P<0.05) aquaretic action characterized by 300-fold increase in urine production
Karumi, Addy and Ugonna et al, 2003[8]	vivo	Aqueous extraction Dose 0.15mg/100g	As diuretic	The extract significantly lowered (p<0.05) serum level of creatinine, bicarbonate, urea, sodium Serum potassium increased (p<0.05)
Jonadet et al, 1990[24]	vitro	Hydro-alcoholic extract Dose was not identified	ACEI	Anthocyanine was responsible for ACEI effect of hibiscus
Sarr et al, 2009[11]	vivo	Butanolic, crude, residual and ethyl extraction Dose was not identified	vasorelaxation	Butanolic extraction had the biggest fraction of anthocyanin and had the greatest vasorelaxant capacity

Adegunloye et al,1996[25]	vivo	Aqueous extraction Dose 20mg/kg	vasorelaxation	Decreased in the mean arterial pressure and it's dose dependant
Obiefuna et al, 1994[27]	Vivo and vitro	Aqueous extraction Doses (0.02-7.68 mg/ml)	vasorelaxation	Significant vasorelxation was observed in vitro experiment and this effect was dose dependatly
Tseng et al, 1997[28] and Tsai et al,2002[29]	vivo	Ethanolic extraction Dose 0.02 mg/kg	antioxidant	Scavenging free radicals And in long term use reducing the blood pressure
Salah et al, 2002[30]	vivo	Methanolic extraction Dose not identified	Calcium channel modulation	Quercetin and euganol chemical constituent of hibiscus were responsible for this activity**
El saadany et al, 1991[31]	vivo	Aqueous extraction Dose 5 and 10%	Cardio-protective	Significant decrease in s-ALT,AST, alkaline , acid phosphatase , total serum protein
Chen et al,2003[32]	vivo	Aqueous extraction Dose 0.5 or 1%	Cardio-protective	Significant reduction in LDL, cholesterol, triglyceride
Gurrola-diaz et al, 2010[33]	RCTs in patients with dyslipidemia associated with metabolic syndrome	Hibiscus powder Dose 100mg/day	Cardio-protective	Significantly ($p<0.02$) reduced total cholesterol and triglyceride levels and increased HDL
Lin et al, 2007[14] and Chen et al2003[32]	vivo	2 capsule of hibiscus/ day	Cardio-protective	Antioxidant ability of hibiscus can inhibited LDL oxidation

RCTs: randomized clinical trials, ALT: alanine transaminase , AST: aspartate transaminase, HDL: high density lipoprotein, LDL: low density lipoprotein, ACEI: angiotensin converting enzyme inhibitor.*Hibiscus found to act as diuretic same as furosemide but with advantage, it found that hibiscus maintain potassium level. ** Hibiscus found to act same as nifidipine.

CONCLUSION

All the studies agreed that *Hibiscus Sabdariffa* can significantly reduce the blood pressure but all the problems that reported in the discussion of the results found is the further evaluation of this herbal remedy to be approved as an effective antihypertensive agent. So the recommendation will be more robust high quality randomized clinical trials to be conducted with a standardized dose of the active ingredient of Hibiscus Sabdariffa to be used on pre-hypertension and stage1 hypertension to avoid withdrawal of participants due to uncontrollable blood pressure and to design such studies with long duration of follow up to detect any adverse effects.

RECOMMENDATION:

As mentioned, Sudan is one of the developing country that 90% of it is community suffering from poverty, so conducted herbal remedies as alternative medicine such as *Hibiscus Sabdariffa* in future become an important.

The conducted studies in this paper did not mention is it safe to use hibiscus with other antihypertensive drugs? This is very important point of view, because some hypertension cases can't outstanding without antihypertensive drugs, so when educated people to add hibiscus in their diet, this question will be the first one community will ask. So further robust clinical trial need to be conducted.

Second question will be, when using hibiscus with other antihypertensive drugs, is this combination will become synergistic? Or partial antagonistic? In other word, is there are possibility that hibiscus and other antihypertensive drugs to compete on the same receptor? The recommendation here will be the capability to answer these questions by conduct laboratory investigation.

Final question and the most important question, can hibiscus be an alternative medicine for hypertension?? All authors agreed that hibiscus is effective as antihypertensive agent, but can it be an alternative? No author answer's this question, so the recommendation is conduct more randomized clinical trial.

In summary the recommendations will be: more robust clinical trial, further laboratory investigation and more research on this herbal remedies.

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