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ANTIHYPERTENSIVE EFFECT OF HERBAL FORMULATION: WITH POSSIBLE MECHANISM OF ACTION.

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Article Info

Novelty Statement:

This study is the first to demonstrate the dose-dependent antihypertensive and hypotensive effects of the polyherbal formulation *Garlina* in vivo, revealing its dual mechanism of action through muscarinic receptor activation, β-adrenergic modulation, and involvement of the nitric oxide (NO)-cGMP pathway. These findings provide novel pharmacological evidence supporting the traditional use of *Garlina* in the management of hypertension and highlight its potential as a multi-target herbal therapeutic.

Abstract

INTRODUCTION: This research work was done to evaluate the in vivo hypotensive and antihypertensive potential of polyherbal product Garlina and determine its receptor activity. Garlina was evaluated for lowering blood pressure in anaesthetized Wistar rats by using BP transducer coupled with Power Lab data acquisition system.

METHODOLGY: Intravenous administration of Garlina produced hypotensive effect in dose-dependent manner (29- 61.1) % fall in MABP at the log doses of 1, 3, 5, 10 and 30 mg/kg in normotensive rats.

RESULTS: The hypotensive effect of Garlina (10mg/kg) was abolished when rats pretreated with atropine sulfate. The same dose of Garlina did not eliminate the hypertensive effect of Phenylephrine (10^{-4} M) but it caused significant fall in MABP when given prior to adrenaline (Adr, 1µg/kg). These data showed that Garlina possess blood pressure lowering activity mediated via muscarinic receptors as well as β-adrenergic pathways.

CONCLUSION: Following the L- NAME administration, Garlina gradually dropped the MABP in 15 minutes. The obtained results indicate that the possible mechanism of action is NO synthesis and NO-cGMP pathway behind the antihypertensive and vasorelaxant effect of Garlina. Therefore it is concluded that provides a rationale to the medicinal use in hypertension.

Keywords: Garlina, Antihypertensive, muscarinic receptors, β- adrenergic pathways, L NAME.

Introduction

Heart diseases represent a predominant cause of mortality around the world. Hypertension (HTN), the primary cause for acute myocardial infarction, accounts for approximately 16.5% of annual worldwide fatalities. Furthermore, it stands as the foremost contributor to the incidence and adverse outcomes associated with cardiovascular diseases (Kamyab R et al 2021). The ESC/ESH guidelines establish hypertension as blood pressure exceeding 140/90 mm Hg, whereas the ACC/AHA's latest 2017 guidelines set a lower threshold for hypertension at blood pressure levels exceeding 130/80 mm Hg. (Arnett DK et al. 2019; Bakris G et al. 2019).Situated in South Asia, Pakistan ranks as the world's fifth most populous country. The healthcare system in Pakistan is divided into a private sector (comprising 70%) and a public sector (making up the remaining 30%). Regrettably, only 27% of the population enjoys comprehensive healthcare coverage, leaving 73% reliant on out-of-pocket payments (Elahi A et al,2023).

According to a national health survey conducted in 2010, it was revealed that In Pakistan, hypertension affected 18% of all individuals and 33% of those over 45. Additionally, it was shown that every third hypertensive person 40 years of age and older was susceptible to a variety of illnesses (Riaz M et al. 2021). In Pakistan, chronic illnesses such as diabetes mellitus, cardiovascular disease, and chronic renal disease frequently precede or coexist with hypertension. Furthermore, a number of behavioral and sociodemographic variables are commonly linked to hypertension, such as obesity, smoking, sedentary lifestyles, and a family history of these illnesses (Dey S et al. 2018).

Throughout human history, herbs have held a prominent position, serving various functions in culinary and medicinal applications. The global adoption of plant-based remedies has grown significantly in the past three decades. One of the primary drivers behind this surge in popularity likely stems from the conviction that diets and herbal preparations based on natural products have been in use for centuries and are generally perceived as safe. Through the assessment of 498 traditional medicines, it has been identified that 136 herb species and 56 combinations of allied herbs demonstrated the intended ability to reduce blood pressure. In certain geographic areas, various acupuncture therapies such as ear acupuncture and the use of seven-star needles, in combination with the application of magnetic forces on specific points, as well as practices like "Qi-gong" involving breathing exercises, have demonstrated their effectiveness. These approaches have significantly contributed to enhancing our clinical methods for treating high blood pressure

(Pan X et al. 2021).

Garlina, created by Hamdard Laboratories (W) Pakistan, is an herbal blend recommended to reduce blood cholesterol levels and prevent the formation of plaque, while also assisting in the management of blood pressure and blood sugar regulation. This formulation is crafted from a combination of five medicinal plants: *Allium sativa*, *Allium cepa*, *Commiphora mukul*, *Nigella sativa*, and *Zingiber officinale* (Sadaf F et al. 2016). The reported activities of the medicinal plants

in garlina are enlisted in the table below. While the separate components of Garlina have shown favorable pharmacological attributes, they do not conclusively endorse the product's cardiovascular protective effects. In light of this, the aim of this research was to explore the hypotensive and anti-hypertensive impacts of Garlina in normotensive rats, with a particular focus on understanding the potential mechanisms underlying its hypotensive effects.

MATERIALS AND METHODS

Drug

Garlina tablets were provided by Hamdard Laboratories (waqf) Pakistan. The dose of Garlina is recommended as two times in a day, equivalent to 20mg/kg. To assess the hypotensive effects, we selected the doses of Garlina at 1, 3, and 5 mg/kg, along with their tenfold higher doses of 10, 30, and 50 mg/kg, as per prior studies (Smart L et al. 2022).

Chemicals

Sigma Aldrich provided NG-nitro-L-arginine methyl ester hydrochloride, or L-Name. The suppliers of acetylcholine and atropine sulfate were E. Merck and C. H. Boehringer Sohn Ingelheim Rhein, Germany, respectively. Adrenaline was procured from Ameer Pharma Pvt Ltd, and Phenylephrine HCl from Atco Laboratories Ltd. Heparin and urethane were purchased from Leo Pharma and Unichem, respectively.

Animals

This study involved the use of normotensive Wistar rats, weighing between 200-240 grams, of both sexes. The animals were housed in a controlled environment at the animal house of Dr. HMI Institute of Pharmacology and Herbal Sciences, Hamdard University, with access to a standard diet and water ad libitum.

Hypotensive evaluation

1.2 g/kg of urethane was administered via intraperitoneal injection, was used to anesthetize the normotensive rats. These animals were cannulated by, trachea to promote respiration, via the jugular vein for the injection of test samples, and by the carotid artery to monitor blood pressure

(Phan TX et al. 2022).

Polyethylene cannulas were employed to inject the test extracts into the right jugular vein, a flush of saline or a 5% Tween-80 solution. The carotid artery was used to measure arterial blood pressure using an arterial cannula connected to a research-grade blood pressure transducer (Harvard, model 60-3003) and a four-channel Harvard oscillograph (Curvilinear, model 50-9307, UK). The animals were maintained at a consistent temperature of 37°C with the help of an overhead heating lamp. Mean blood pressure was calculated by summing the diastolic blood pressure and one-third of the

pulse width. Changes in blood pressure were expressed as a percentage of the control values obtained immediately before the administration of the test substance. Acetylcholine (1µg/kg, sourced from E. Merck) served as the positive control in these experiments.

Acute antihypertensive activity

The evaluation of the acute antihypertensive effect in normotensive rats involved measuring the mean arterial blood pressure, following the same invasive method described in the hypotensive activity. In a nutshell, once the animals were cannulated, they were allowed a 30-minute stabilization period. An inhibitor of nitric oxide synthase, L-NAME, was intravenously administered at a dose of 20mg/kg to induce hypertension (Razzaq MA et al. 2023). When the mean arterial blood pressure (MABP) induced by L-NAME had reached the desired level, Garlina was injected at a dose of 10 mg/kg through the jugular vein. Changes in blood pressure were continuously recorded via a blood pressure transducer (Sadaf F et al. 2023).

2.5. Determination of receptor activity

To investigate the mechanism of action of Garlina, acetylcholine (Ach 10^{-6}M), atropine (Atr 10^{-4} M), adrenaline (Adr 10^{-6}M), and phenylephrine (P.E 10^{-4}M) were employed to determine if the hypotensive effect is mediated through cholinergic or adrenergic pathways.

2.5.1 Via Cholinergic pathway

Urethane, administered at a dose of 1.2-1.5g/kg through intraperitoneal injection, was used to anesthetize Wistar rats weighing between 200 and 250 grams. These rats were cannulated, and arterial blood pressure was measured, as previously described. Following a stabilization period of 15-20 minutes, atropine (Atr $^{10\text{-}4}$ M), a cholinergic antagonist, was introduced. To confirm its blocking effect, acetylcholine (Ach $^{10\text{-}6}$ M), a cholinergic agonist, was subsequently administered. Then, Garlina at a dose of 30mg/kg was given, and the resulting changes in mean arterial blood pressure were recorded, in accordance with the methodology (Saleem R et al. 2016).

2.5.2 Via Adrenergic pathway

The procedure is same as described by (Joshi SV et al. 2020) with slight modification. Briefly, the rat was cannulated and allowed it to stabilize for 15- 20 minutes, then Garlina was administered at the dose of 30mg/kg prior to ∞- selective, Phenylephrine (P.E. 10^{-4}M) and non- selective, Adrenaline (Adr 10^{-6}M) adrenergic agonists. Administration of Garlina was supposed to be attenuated the hypertensive effect produced by P.E and Adrenaline

2.6. Statistical analysis

The data were analyzed using the Software of SPSS version 20. The results are presented as mean ± standard error mean (SEM) by dependent sample t- test and were considered to be significant at $p< 0.05$.

RESULTS:

Our findings reveal that the hypotensive impact of Garlina, administered intravenously at doses of 1, 3, and 5mg/kg, resulted in a dose-dependent fall in Mean Arterial Blood Pressure (MABP) in anesthetized rats. However, at higher doses (i.e., 10, 30, and 50mg/kg), there was a comparable effect on the percentage reduction in systolic and diastolic blood pressure, with the 10mg/kg dose of Garlina demonstrating a more pronounced result. It's worth noting that the duration of action of all doses did not exhibit a strong dose-dependency, as indicated in Table 2. Specifically, at doses of 1, 3, and 30mg/kg, the effect was short-lived, with systolic and diastolic blood pressure returning to normal within a minute. In contrast, the hypotensive effect at doses of 5, 10, and 50mg/kg persisted for approximately 2 to 4.5 minutes (see Table 2 for details). The results revealed that the Garlina (10mg/kg), following the L- NAME injection, caused 42.41% decrease in blood pressure from 113.99 mmHg ± 8.23 to 65.66 mmHg ± 4.85 just after 0.15 minutes. It was further dropped to 47.68%, 54.18%, 62.07% and 69.65% and finally to 79.91% after 0.5, 1.0, 5, 10 and 15 minutes respectively.

As it is observed in table 3, the hypotensive effect of Garlina was observed when animals pretreated with Atropine ($^{10-4}$ M), Adrenaline and Phenylephrine (19).The hypotensive effect of Garlina was blocked when animal pretreated with Atropine ($^{10-4}$ M), which shows that vasorelaxatory and hypotensive effect of Garlina may be mediated by muscarinic receptors similarly Garlina attenuates the effect of Adrenaline and did not abolish the effect of α- selective adrenergic receptor (Phenylephrine) as shown in table 2. It was suggested that the hypotensive response of Garlina was mediated through cholinergic and β- adrenergic receptors or a mechanism that is similar to β-adrenoceptor.

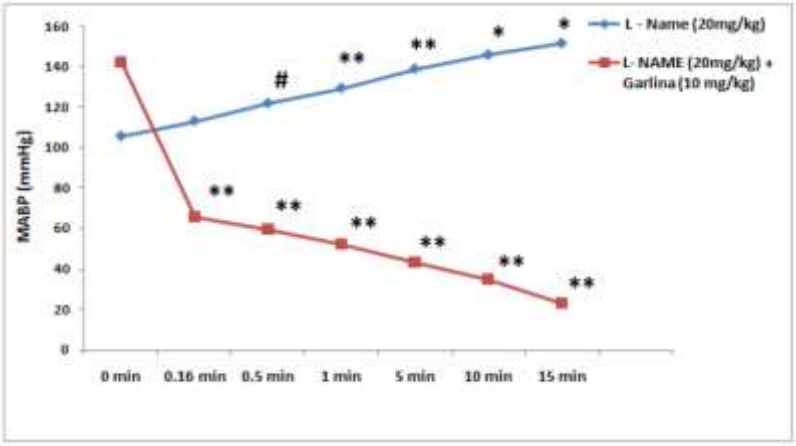

Figure- 1 Effect of Garlina on the mean arterial blood pressure in L- NAME induced hypertensive rats

Each point represents the mean ± SEM (n=3); *p < 0.0005, **p< 0.005 and $^{\#}$p< 0.025 significantly different when compared to the initial value (0 minute

TABLE 1: Pharmacological properties of the components of Garlina

Name	Pharmacological activities	References
***Allium sativa* (garlic)**	Antiatherosclerotic, Antihyperglycemic, antitumor, antimicrobial, antifungal, anti-aging, anti-cancer, antioxidant antihypertensive activity	(Nasir A et al. 2020)
***Allium cepa* (onion)**	Inhibits platelet aggregation hypoglycemic, neuroprotective, anti-convulsant, anti-hypertensive,	(Zhao X-X et al. 2021)
***Commiphora mukul* (guggul)**	used in the treatment of rheumatoid arthritis, cardiovascular diseases, obesity, hemorrhoids, kidney diseases and have anti-diabetic and antihyperlipidemic potential	(Garang Z et al. 2023)
***Nigella sativa* (black cumin)**	Neuroprotective activity, gastro protective activity, cardio protective activity, anti-dyslipidemia, anti-obesity activity, anti-inflammatory activity	(Adam SH et al. 2023)
***Zingiber officinale* (ginger)**	Used in inflammation, antioxidant, antiplatelet, hypotensive and hypolipidemic effects	(Dissanayake KGC et al. 2020)

TABLE 2: Effect of different doses of Garlina on % reduction in Mean Arterial Blood Pressure (MABP)

Dose (mg/kg)	% fall in MABP (mmHg)	Duration (sec)
1mg	28.85±2.36*	30.33±14.8
3mg	37.24±1.01*	23.9±129.3
5mg	40.82±4.22*	268.40±140.6
10mg	61.16±4.7*	171.25±50.51
30mg	58.13±5.7*	57.80±23.42

TABLE 3: Effect of Garlina on Muscarinic and Adrenergic Receptors

Muscarinic Receptor		**α – selective Adrenergic Receptor**		**Non selective Adrenergic Receptor**	
Parameters	**% Change**	**Parameters**	**% Change**	**Parameters**	**% Change**
Ach (10^{-6}M)	-43.5 ± 0.2$^{\$}$	P.E (10^{-4}M)	103.3 ± 1.3$^{\#}$	Adr (10^{-6}M)	69.0± 2.4**
Garlina(10mg/kg)	-61.2 ± 5.0*	Garlina(10mg/kg)	-61.2 ± 5.0*	Garlina(10mg/kg)	-61.2± 5.0*
Atr (10^{-4}M) + Ach (10^{-6}M)	2.8 ± 0.6*	Garlina(10mg/kg) + P.E (10^{-4}M)	160.8±11.5***	Garlina(10mg/kg) + Adr (10^{-6}M)	-25.3± 5.0$^{\$}$
Atr (10^{-4}M) + Garlina(10mg/kg)	2.1 ± 0.3**				

DISCUSSION:

Hypertension (HTN) is an escalating public health concern in less-developed countries (Omar SM et al. 2020) and its prevalence continues to increase over time. While several antihypertensive drugs have been developed to combat rising blood pressure, the adherence to these treatment regimens, including concerns about medication costs, side effects, and the accessibility and availability of drugs, diverts the interest of a significant portion of hypertensive patients. It's important to remember that a wide range of phytochemicals found in plants have been shown to have protective effects against hypertension. Over the past three decades, there have been extensive efforts to explore indigenous medicinal plants with hypotensive and antihypertensive therapeutic potential (Azizah N et al. 2021). Numerous theories have been proposed to explain how the human body maintains blood pressure. The renin-angiotensin-aldosterone system is one of them. The reduction of vascular vasoconstriction is brought about by inhibition of the Angiotensin-converting enzyme, or "ACE" (Tang F et al. 2021). Secondly blockade of Ca^{2+} channels in vascular endothelium are also responsible for the reduction of hypertension. Reduction of blood pressure is also taken by the inhibition of sympathetic and activation of parasympathetic nervous system. Vasodilation is the outcome of ACh binding to muscarinic receptors on smooth muscle and/or endothelium. By disrupting the heart's sympathetic activity, antagonists of norepinephrine and adrenaline at β adrenoceptors lower heart rate and myocardial contractility, which lowers cardiac output and blood pressure (Borovac JA et al. 2020).

The findings of Garlina are proved these claims as a hypotensive effect (Table 1). The constituents of Garlina are proved in various studies for their hypotensive and antioxidant effects by different mechanisms. The mechanism by which Nigella sativa is thought to lower blood pressure has been suggested by a number of studies. These mechanisms include diuretic activity, calcium channel blockade, inhibition of the angiotensin-converting enzyme (ACE), increased cardiac heme oxygenase-1 activity, prevention of plasma nitric oxide loss, antioxidant activity, and cardiac depressant activity (Maideen NM et al. 2021).

Allium cepa is also shown to reduce blood pressure by a reducing oxidative stress and inhibition of Ca^{2+} influx in the cells of vascular smooth muscle (Galavi A et al. 2021). Moreover, *Zingiber officinale* reduces blood pressure by blocking Ca^{++} channels and stimulating muscarinic receptors, both of which have a dual inhibitory impact. This work offers a solid molecular foundation for the use of ginger in the treatment of hypertension and palpitations (Mashabela MN et al. 2023).

Allium sativum lowers blood pressure by decreasing the formation of endothelin 1 and angiotensin II. It also includes a number of active sulfur compounds that have been demonstrated to stimulate endothelium-constricting and -relaxing factors. It has also been demonstrated that allium sativum increases the synthesis of hydrogen sulfide (H2S) and nitric oxide (NO), which ultimately results in vasodilation (El-Saber Batiha G et al. 2020). Though *Commiphora mukul and Zingiber officinale* have been reported for their hypolipidemic effects and synergistically contributed to the hypotensive efficacy of Garlina.

The vasorelaxant effect and activation of muscarinic receptors as shown in fig. 3, have direct link with vascular smooth muscles (Shahlehi S et al. 2021). The stimulation of endothelium nitric oxide synthase (NOS) results in nitric oxide release, leading to vasodilation and produces hypotensive effect of Garlina (Janaszak-Jasiecka A et al. 2023).

CONCLUSION

In summary, the poly-herbal formulation Garlina exhibited no noteworthy signs of toxicity following a single oral administration. The observed hypotensive and anti-hypertensive effects of Garlina, attributable to the stimulation of nitric oxide production, affirm the beneficial properties of the plants comprising Garlina, as mentioned previously.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

Data Availability:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval:

The Dr. HMI Institute of Pharmacology and Herbal Sciences Ethical Committee at Hamdard University granted ethical approval for the experimental methodology (Ref No. AEC-17-01) which followed widely accepted standards for ethical treatment and use of animals.

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