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ORIGINAL RESEARCH article

Hypotensive effect of yeast in the hypertensive rat model

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Abstract: Elevated arterial blood pressure is the most important public health problem in developed countries. It often leads to lethal complications if left untreated. Brewer's yeast is celebrated for its various beneficial effects, including a possible hypotensive effect. Thus, the anti-hypertensive effects of brewer's yeast were investigated. The hypertensive model was done by a once-weekly intraperitoneal injection of dexamethasone at a dose of 25 mg/kg combined with drinking a 1.0% sodium chloride solution containing 0.2% KCl and 2.0% glucose for six weeks. The blood pressure was measured by the rat carotid artery cannulation preparation. Different doses of brewer's yeast dissolved in distilled water were injected into the internal jugular vein, with measurement of blood pressure at each time. To explore the mechanism of the hypotensive effect of yeast, the yeast cardiac effect was verified by the use of isolated perfused rabbit heart preparations using different antagonists. It was found that dexamethasone elevated systolic blood pressure to 178.3±11.6 and diastolic blood pressure to 133.3±16.6 from normal levels of 115.0±9.1 for systolic and 74.0±4.1 for diastolic. The gradual increase in intravenous yeast doses ranging from 0.05 to 0.40 effectively lowered systolic and diastolic blood pressure in rats with normal pressure, bringing them to approximately 80.0±05.6 mmHg for systolic and 40.0±3.5 mmHg for diastolic. While doses exceeding 0.04 resulted in a drop in systolic pressure to 60.0±3.9 mmHg, diastolic pressure became unrecordable. The administration of the 0.20 dose resulted in unrecordable blood pressure. In hypertensive rats, a decrease in blood pressure was observed with doses ranging from 0.60-1.0 mg, leading to a reduction to 110.0±2.8 mmHg for systolic and 52.0±9.9 mmHg for diastolic pressures. Doses exceeding 1.0 mg further lowered systolic and diastolic pressures to 20.0±3.9 mmHg. There was a mild increase in heart rate with no change in cardiac force of contraction. This effect was not mediated through beta, calcium receptors, or the histamine effect. The findings show that the yeast has a dose-dependent blood pressure-lowering effect. The mechanism of the chronotropic effect is possibly due to its direct action.

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Introduction

Hypertension is a pervasive health issue affecting millions of individuals worldwide. Defined by elevated blood pressure levels, a systolic BP ≥ 140 mmHg, and/or diastolic BP ≥ 90 mmHg [1], hypertension is a silent precursor to numerous cardiovascular diseases, including stroke, heart attack, and kidney failure [2]. As a global health concern, it demands thorough investigation and innovative approaches for management and prevention. The quest for natural remedies to mitigate hypertension has led researchers to explore unconventional sources, and one such intriguing candidate is yeast. Yeast, a unicellular fungus, is renowned for its role in fermentation processes in the food and beverage industry [3]. However, recent studies have shed light on its potential hypotensive effects, offering a promising avenue for those seeking alternative strategies to manage blood pressure. Thus, this study aims to explore and elucidate the potential hypotensive effects of yeast on blood pressure in rat models.

Materials and methods

This experimental investigation (n=20 Sprague-Dawley rats), comprising males within a weight range of 190 g to 300 g, was used (10 control group and 10 dexamethasone-treated group). Rats were obtained from the local Central Animal House, University of Benghazi, Benghazi, Libya. Rats were kept in standard laboratory conditions (12hrs/12 hrs of light/dark cycle, and 22.0±2.0 ^{0}C). The rats were fed standard commercial laboratory chow and were allowed to adapt to new housing environment conditions for one week before treatment. The ethical approval to conduct this study was obtained from the Animal Use and Ethics Committee, Faculty of Medicine, University of Benghazi, Benghazi, Libya. Hypertension was induced through a carefully structured protocol involving weekly administration of dexamethasone at a dosage of 25 mg/kg/week via intraperitoneal injection [4]. This treatment regimen spanned six weeks and was complemented by a solution consisting of 1.0% sodium chloride (NaCl), 0.2% potassium chloride (KCl), and 2.0% glucose. The addition of KCl aimed to counteract the potassium-depleting effects of dexamethasone, while the inclusion of glucose was intended to enhance NaCl intake. To monitor blood pressure levels, the experimental approach incorporated the carotid artery cannulation method [5, 6]. Rats were anesthetized with urethane at a dose of 1.0 g/kg administered intraperitoneally. A cannula, linked to a blood pressure transducer, was delicately inserted into the carotid artery to facilitate the recording of blood pressure data. The administration of varying doses of yeast was carried out through a cannula positioned in the internal jugular vein. Doses range from 0.05-2.0 mg. Blood pressure measurements were systematically recorded and displayed using a Washington 400 MD 2C recorder, enabling the construction of dose-response curves.

To explore the mechanism of the hypotensive effect of yeast, the mechanism of the action of the yeast on the cardiac contraction and heart rate was studied by using of isolated rabbit heart model [Langendroff preparation]. This preparation was set up as described by Burns [7]. The animals were killed. The thorax was opened and the heart was removed as quickly as possible making sure that a good length of the stump of the aorta was left, and put in a petri dish containing Krebs solution prewarmed to 37 ^{0}C, and saturated with a mixture of 5.0% CO_2 in oxygen. The whole heart was perfused through a cannula inserted into the aorta. The flow was adjusted, so that, there was perfusion without excessive distension of the ventricles [perfusion pressure about 40 mmHg]. The heart was connected using a clip attached to the tip of the left ventricle through pulleys to a force-displacement transducer and recording device. Drug solutions were injected through rubber tubing directly into the aorta. The whole preparation was enclosed in a constant temperature chamber [8]. 0.2 ml of the following drugs was injected with the record of the heart rate and force of contraction after each injection. Captopril [1×10^{-6}M]. Adrenaline

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[1×10^{-5}M], calcium chloride [10 µm], and yeast at different doses (0.2-1.6 mg). The tissue was allowed to equilibrate for 10 min between doses. Dose-response curves were obtained for yeast doses. The heart rate and force of contraction were retested again by adding the following blockers before injecting the previously mentioned drugs; propranolol [1×10^{-5} M], verapamil [1×10^{-8} M], and cimetidine [10 µm], to record the possible antagonizing effects to the yeast cardiac action.

Statistical analysis: A test of significance was carried out using a one-way analysis of variance (ANOVA). The degree of significance was determined by using the Turkey test. HSD test, as well as the Tamhane test for dependent samples. A probability value of less than 0.05 was considered significant.

Results

Effect of yeast on blood pressure: The experiment showed that dexamethasone led to a high statistical increase in systolic blood pressure (SBP) as well as in diastolic blood pressure (DBP), with $P < 0.01$, (178.3±11.6) for SBP and (133.3±16.6) for DBP as compared to normal, which was 115.0±9.1 for SBP and 74.0±4.1 for DBP (**Figures 1a** and **1b**). Moreover, there were high statistical reductions in SBP as well as in DBP, with $P < 0.01$ by the gradual increase in the intravenous dose of the yeast in the rat cannulation method. It was noted that doses ranging from 0.05 to 0.4 effectively lowered systolic and diastolic blood pressure in rats with normal pressure, bringing them to 80.0±5.6 mmHg for SBP and 40.0±3.5 mmHg for DBP. However, at doses exceeding 0.04, the SBP dropped to 60.0±3.9 mmHg, and the DBP became unrecordable. Furthermore, the administration of a 0.20 dose resulted in unrecordable blood pressure. Nevertheless, a decrease in blood pressure was observed in hypertensive rats with a dose ranging from 0.6 to 1.0 mg, leading to a reduction to 110.0±2.8 mmHg for SBP and 52.0±9.9 mmHg for DBP. Doses exceeding 1.0 mg further lowered SBP and DBP to 20.0±3.9 mmHg. Additionally, administering a dose of 7.0 resulted in SBP and DBP becoming unrecordable.

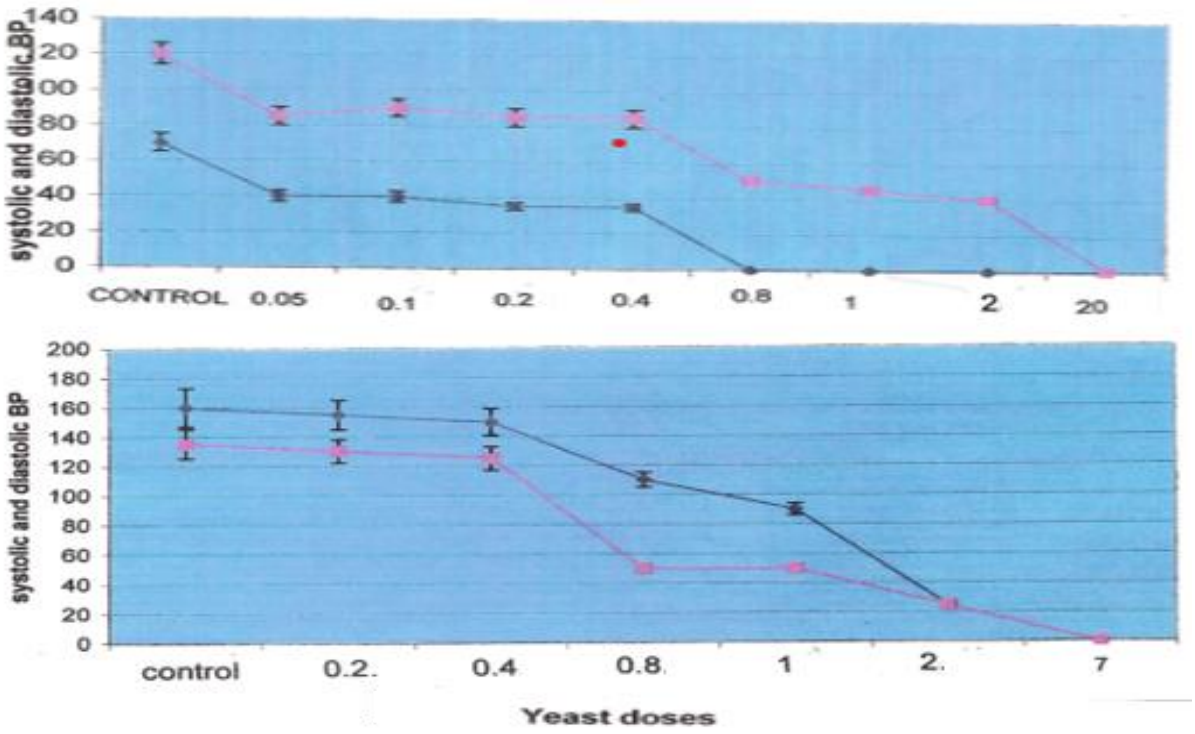

Figure 1: Effect of yeast on blood pressure of normal rats (1a) and hypertensive rats (1b)

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Effect of yeast on heart rate and force of contraction: It was observed from the experiment that the yeast at doses of 0.2-1.6, which show hypotensive effect, had no effect on cardiac force of contraction on isolated rabbit heart preparation, but had mild positive chronotropic effect [mild increase in heart rate] (**Figures 2** and **3a**). This mild chronotropism was not abolished with beta receptor antagonist (propranolol) (**Figure 3c**), calcium receptor antagonist (verapamil) (**Figure 3e**), or H_2-receptor antagonist (cimetidine) (**Figure 3g**). The effect of yeast was compared with captopril which showed no effect on heart rate and force of contraction. The antagonizing effect of propranolol to adrenaline (**Figure 3d**) and verapamil to calcium chloride (**Figure 3f**) were also investigated.

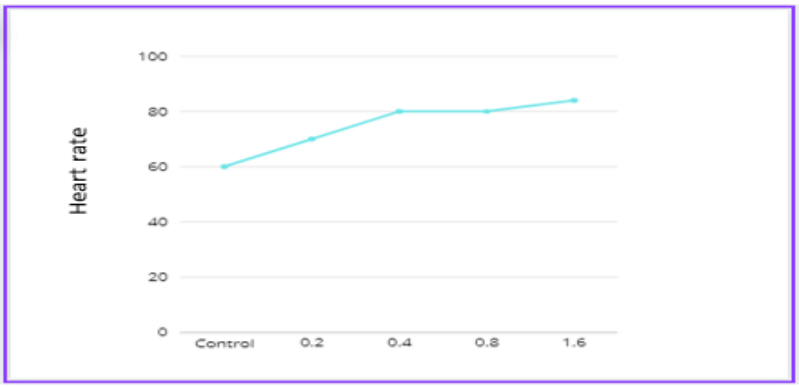

Figure 2: Relationship between yeast doses and heart rate

Figure 3a: Effect of yeast at different doses

Figure 3b: Effect of captopril at two different doses

Figure 3c: Effect of yeast at a dose of 1.6 alone and with the addition of 1 x 10^{-5} propranolol

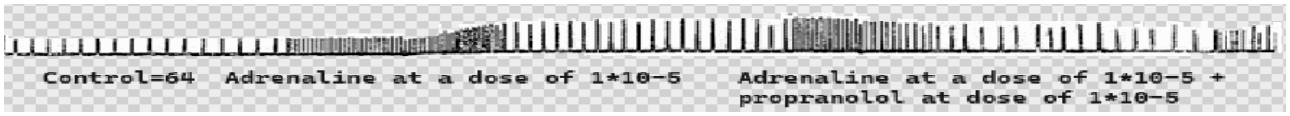

Figure 3d: Effect of adrenaline at a dose of 1 x 10^{-5} alone and with the addition of 1x10^{-5} propranolol

Figure 3e: Effect of yeast at a dose of 1.6 mM alone and with the addition of 1x10^{-8} verapamil

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Figure 3f: Effect of calcium chloride at a dose of 10 mM alone and with the addition of $1x10^{-8}$ verapamil

Figure 3g: Effect of yeast at a dose of 1.6 mM alone and with the addition of 10 mM cimetidine

Discussion

The induction of hypertension in rat models involved the administration of dexamethasone. The hypertensive response can be attributed to its impact on several physiological mechanisms. Glucocorticoids, such as dexamethasone, play a crucial role in regulating vascular tone and sodium balance. Dexamethasone enhances sodium reabsorption in the renal tubules, leading to increased extracellular fluid volume [9]. This expansion of fluid volume, combined with the direct effects on vascular smooth muscle, contributes to elevated blood pressure levels [10]. Moreover, dexamethasone has been associated with the suppression of nitric oxide (NO) production. NO acts as a vasodilator, promoting relaxation of blood vessels. The reduction in NO availability due to dexamethasone administration can further contribute to increased vascular resistance and blood pressure elevation [11]. In this investigation, yeast exhibited a noteworthy antihypertensive impact in a dose-dependent manner within the dexamethasone-induced hypertension model. These findings align with human research conducted in Iran, which demonstrated that the addition of 1800 mg/day of brewer's yeast to standard treatments has been identified as having a moderate positive impact on systolic and diastolic blood pressure [12]. It also agreed with another research conducted in Japan and showed a hypotensive effect in the spontaneous hypertensive rat model [13]. Various theories exist regarding the mechanism through which brewer's yeast affects blood pressure. The blood pressure-lowering attributes of brewer's yeast are ascribed to its biological peptides, potassium, magnesium, and calcium [13, 14]. Notably, the biological peptide KRF814, derived from the hydrolysis of brewer's yeast by alkaline phosphatase, is believed to reduce the activity of angiotensin-converting enzyme, potentially leading to a decrease in blood pressure [13]. Therefore, the potential mechanism of yeast's action may be attributed to its angiotensin inhibitory peptides. Moreover, the hypotensive effect of brewer's yeast was proven through a demonstration highlighting the impact of a fraction with a molecular weight below 3 kDa. This particular fraction, which consists of tri- and tetra-peptides containing hydrophobic amino acid residues such as SPQW, PWW, and RYW, exhibited a significant reduction in systolic, diastolic, and mean blood pressure in spontaneously hypertensive rats [16]. Furthermore, it displayed the most potent antioxidant effect among the tested components [16]. Another potential contributing factor to the antihypertensive effect of yeast could be its elevated dietary fiber content [17]. Prior studies have reported that the cell wall fraction of yeast contains substantial dietary fiber, exhibiting a hypocholesterolemic effect [17]. This becomes significant as it has previously been established that the amelioration of hyperlipidemia contributes to a reduced risk of hypertension.

On the other hand, the mechanism of the action of the yeast on the cardiac contraction and heart rate was studied in this work by using an isolated rabbit heart model. It was found that the yeast had no effect on the cardiac force of contraction at the hypotensive dose but had a mild increase in heart rate. It also compared its effect with captopril, which had no effect either in the cardiac force of contraction or the heart rate. This result was in contrast

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to a previous study, which found that ACE-I produces a negative inotropic effect [18]. The mild positive chronotropic effect of the yeast was further studied by using different antagonists such as beta-blockers (propranolol), calcium channel blockers (verapamil), and antihistamines (cimetidine). In this study, propranolol inhibited the cardiac stimulant effect of adrenaline but did not affect the yeast mild chronotropism. This may suggest that yeast action is not beta agonist-mediated. Also, verapamil led to inhibition of the cardiac stimulant effect of calcium chloride but did not affect the yeast cardiac effect. This also suggested that the yeast action is not calcium-mediated. Moreover, histamine produces an increase in left ventricular contractility, coronary flow, total cardiac output, and also sinus rate [19]. We found that antihistamine-(H2) blockers alone did not affect cardiac function. This result is in agreement with that obtained by earlier studies [20]. It was also found that the H2 blockers, which antagonized the effect of histamine on all measured parameters [21], did not affect on the yeast cardiac chronotropic action. This suggests that the yeast chronotropic cardiac effect is not through histamine-like action. Thus, the mild chronotropic effect may be due to the direct action of the yeast.

Conclusion: This study showed that the yeast had a dose-dependent blood pressure-lowering effect. There was a mild increase in heart rate which was not mediated through beta receptor agonist, calcium receptor agonist, or histamine effect, but it may be due to yeast direct effect with no change in cardiac force of contraction.

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Author contribution: AMA conceived, designed the study, and analyzed data. AMA, FE & SMA collected data. AMA, AAB, AFB & AGA drafted and revised the manuscript. All the authors approved the final version of the manuscript and agreed to be accountable for its contents.
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Ethical issues: Including plagiarism, informed consent, data fabrication or falsification, and double publication or submission have completely been observed by authors.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author declarations: The authors confirm that all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.