

Effect of Oral intake of Sodium Benzoate on Serum Cholesterol and Proinflammatory cytokine (Tumor necrosis factor alpha [TNF- α] and Interleukin-6 [IL-6]) levels in the heart tissue of Wistar rats

ABSTRACT

The *in vivo* effect of oral administration of varying concentrations (150, 250, 500mg/kg body wt.) of sodium benzoate (a known preservative in the food, cosmetic and pharmaceutical industry) on serum cholesterol and proinflammatory markers in heart tissue of wistar albino rats were investigated. The oral intake was administered at 24 hour intervals for 7, 14, 21 and 28 days. The groups were labelled; control (group 1), 7days (group 2), 14days (group 3), 21 days (group 4) and 28days (group 5). The rats were fed normal diet *ad libitum* and blood sample for the determination was taken at the end of the duration. For serum cholesterol, the result obtained for sodium benzoate concentrations administered showed significant ($p \leq 0.05$) decrease in cholesterol levels at group 5 for 250mg/kg body wt. and grp 2, 3, 4 and 5 for 500mg/kg body wt of experimental rats. The proinflammatory cytokines TNF- α and IL-6 of heart tissue showed significant decrease at grp 4 and 5 for 250mg/kg body wt and 2, 3, 4 and 5 for 500mg/kg body wt. values were all compared to control. These findings suggest modulation of the inflammatory pathway due to administration of the preservative.

Key words: Sodium benzoate; Cholesterol; Serum; Proinflammatory cytokines.

23 INTRODUCTION

24 The investigations of constituents of blood and organ tissue of mammals have continually played
25 a valuable role in the normal functioning assessment of living organisms. Changes from the
26 normal levels have been observed in disease conditions [1]. The effects of various compounds on
27 biochemical parameters of experimental animals have been applied in assessing the safe use of
28 compounds in products consumed. Sodium benzoate (C_6H_5COONa) is widely applicable as a
29 preservative in several products consumed by man [2, 3, 4, 5]. Sodium benzoate metabolizing
30 occurs in the mitochondria matrix, it is metabolized by conversion to hippurate in two steps:
31 Sodium Benzoate enters the mitochondria and is converted to benzoyl CoA by an ATP-
32 dependent acid, butyrate CoA ligase. Then benzoyl CoA is subsequently converted to hippurate
33 by glycine N-acyltransferase, and then exits the mitochondria. Ingestion of sodium benzoate
34 causes a rise in both serum benzoate and hippurate level [6]. Sodium benzoate is also a
35 component of ucephan, a food and drug administration approved drug used in the treatment of
36 hepatic metabolic defects associated with hyperammonemia such as urea cycle disorder [7, 8]. It
37 has been reported that 2% solution of sodium benzoate in drinking water is safe for lifelong
38 treatment in mice without any noticeable side effects [9]. Recent studies have shown that sodium
39 benzoate is useful in protecting mice from relapsing–remitting experimental allergic
40 encephalomyelitis [10] and that it is also capable of inhibiting the expression of various
41 proinflammatory molecules from activated glial cells [10]. Several studies on the short and long
42 term effects of sodium benzoate have reported adverse effects due to both chronic and
43 subchronic intake of sodium benzoate [11, 12]. Some reports suggest the absence of negative
44 consequence of sodium benzoate intake [9, 13]. The upper limits of benzoate allowable in foods
45 vary with 0.1% reported for United States of America, while a range of 0.15 to 0.25% had been

46 reported for other countries of the world [14]. For European countries, the limit reported range is
47 from 0.015 to 0.5% [15]. There are thus variations in the acceptable limits of these preservatives
48 in foods. It therefore follows that sodium benzoate could be assimilated widely by consuming a
49 wide range of food products intentionally preserved with it. The present report addressed the
50 effects of oral administration of sodium benzoate on serum cholesterol, and proinflammatory
51 cytokines in heart tissue. The findings in this study indicate that sodium benzoate may be useful
52 in modulating the downstream signaling pathway.

53

54 **MATERIALS AND METHOD**

55 The experimental analysis was carried out in the Department of Biochemistry Research
56 Laboratory, University of Port Harcourt, Choba, Rivers State, Nigeria. The study duration was
57 for a period of one month, twenty eight days being the longest duration. The animals were
58 purchased from the Department of Biochemistry, Animal House. Sodium benzoate was
59 purchased from May & Baker Ltd., England. The reagent for cholesterol determination was
60 purchased from Agape Diagnostics, Switzerland. TNF alpha and IL-6 kits were purchased from
61 Elabscience, Donghu Hi-Tech Development Area, Wuhan, China. while all other reagents were
62 of analytical grade. An approval was given by the Institution ethics committee for the
63 commencement of this study.

64

65 **Animals**

66 A total of sixty-six (66) wistar albino rats, with an average weight of 140g were obtained from
67 the animal house of the Department of Pharmacology, University of Port Harcourt. They were

68 maintained on normal diet *ad libitum*, grouped into five (5), and housed in stainless steel cages in
69 a well ventilated room under 12h light/dark cycle. The sodium benzoate concentrations were
70 150mg/kg body wt., 250mg/kg body wt and 500mg/kg body weight. The rats were divided into
71 five groups namely G1 (control group), G2 (7days), G3 (14days), G4 (21days) and G5 (28days).
72 The varying concentrations of sodium benzoate were administered orally in 1ml portions at 24 h
73 intervals for the duration of the experiment (7, 14, 21 and 28 days). At the end of the
74 experimental duration the rats were sacrificed.

75

76 **Sample collection**

77 The rats were anaesthetized with diethyl ether and dissected for blood collection. Blood samples
78 collected were allowed to coagulate in sample bottles and centrifuged at 2500rpm for 10 mins
79 and stored at 4°C and the serum obtained was used to estimate cholesterol. After blood
80 collection, the liver and heart were excised, weighed and rinsed in ice cold normal saline and
81 transferred into ice cold sample containers for determination of the proinflammatory cytokines;
82 interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF- α) assay.

83

84 **Determination of cholesterol**

85 **Principle**

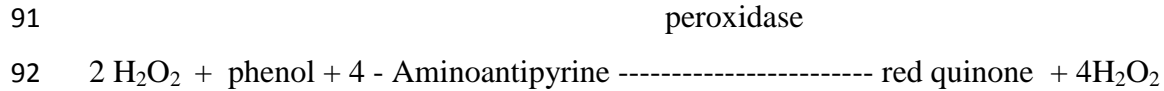
86 Enzymatic colorimetric determination of total cholesterol

87 Cholesterol esterase

88 Cholesterol ester + H₂O ----- cholesterol + fatty acids

89 cholesterol oxidase

90 Cholesterol + O₂ ----- 4-chloesten-3-one + H₂O₂



94 **Determination of TNF-alpha**

95 This ELISA kit applies to the in vitro quantitative determination of Rat TNF- α concentrations in
96 serum, plasma and other biological fluids. The kit is specific for rat TNF-alpha detection. The
97 ELISA kit uses the sandwich-ELISA principle.

98
99 **Determination of Interleukin-6**

100 This ELISA kit applies to the in vitro quantitative determination of Rat IL-6 concentrations in
101 serum, plasma and other biological fluids. The kit is specific for rat Interleukin-6 detection. This
102 ELISA kit uses the Sandwich-ELISA principle.

103
104 **Statistical analysis**

105 All data were subjected to statistical analysis. The values were reported as mean \pm standard error
106 of mean (S.E.M), and analysed by one-way analysis of variance (ANOVA). ANOVA was used
107 to test for differences between treatment groups using statistical package for social sciences
108 (SPSS) version 20. The results were considered significant at P-values of less than 0.05, that is,
109 at 95% confidence level ($P < 0.05$).

110

111 **RESULT**

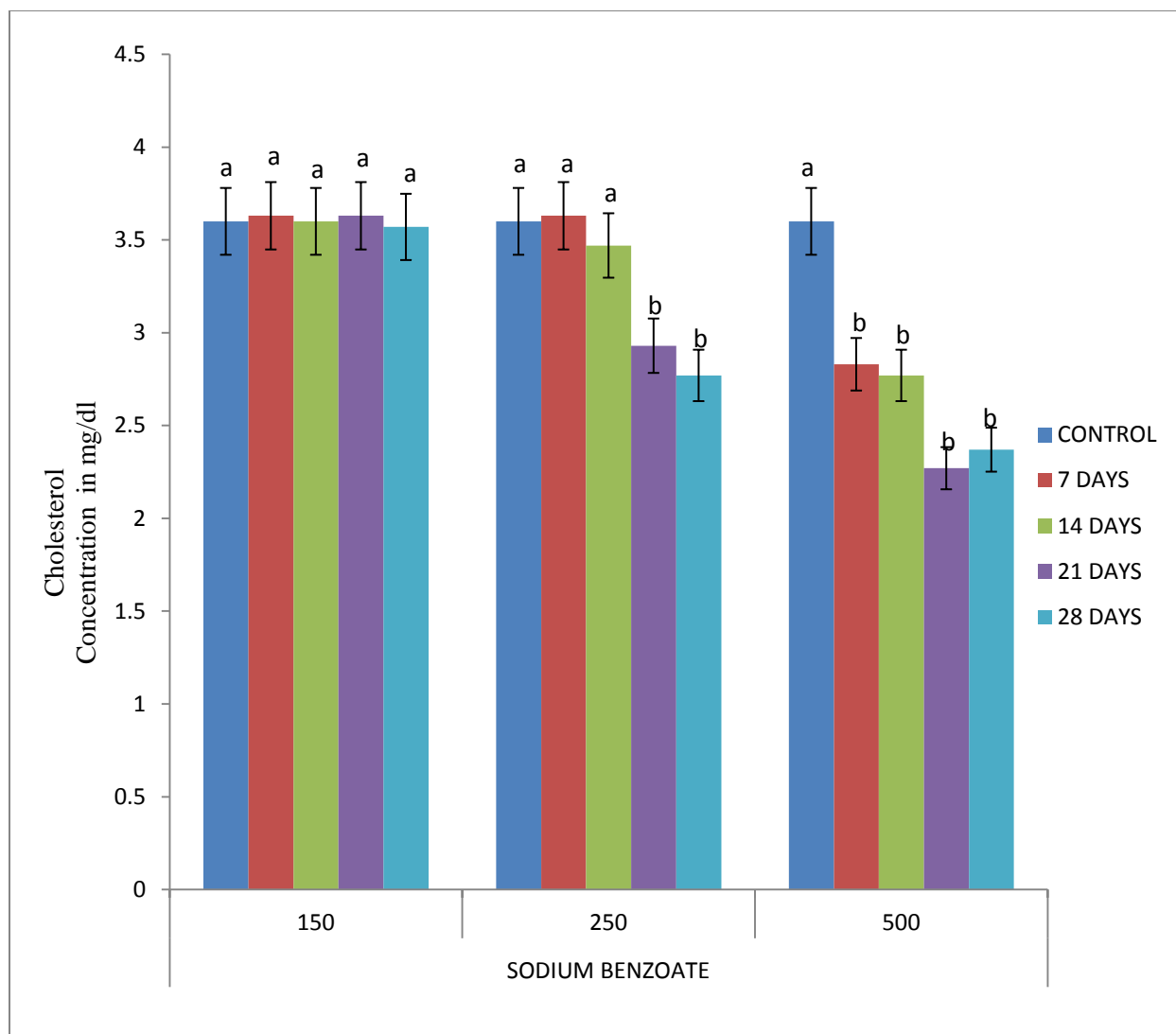
112 The result of the effect of Sodium benzoate on Serum Cholesterol, Interleukin-6 and Tumor
113 necrosis factor – α in heart tissue of wistar rats are shown in fig 1, 2 and 3.

114 The cholesterol level of experimental rats in group 2, 3, 4 and 5 showed sodium benzoate had no
115 significant difference for 150mg/kg body wt. but significantly ($p \leq 0.05$) decrease was observed in
116 group 5 for 250mg/kg body wt. and group 2, 3, 4 and 5 for 500mg/kg body wt. values were all
117 compared to the control.

118

119

UNDER PEER REVIEW



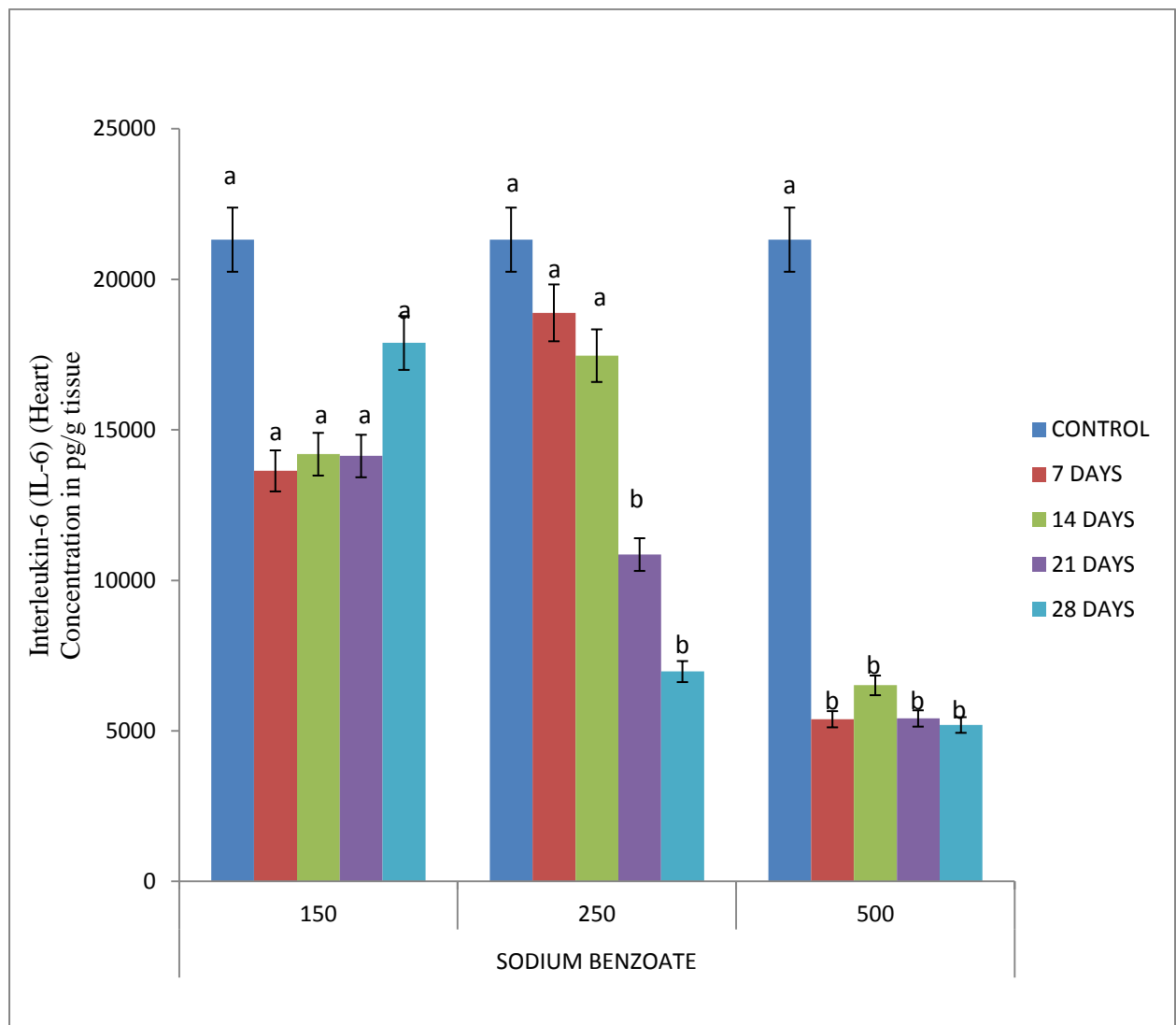
120
121

122 Fig 1: Effects of varying concentrations of sodium benzoate on cholesterol levels in serum.

123 Values are means \pm Standard Error Mean (SEM). Values with different superscript are
 124 statistically significant at ($p \leq 0.05$). Superscript (a,b) compares 7 Days, 14 Days, 21 Days and 28
 125 Days to control.

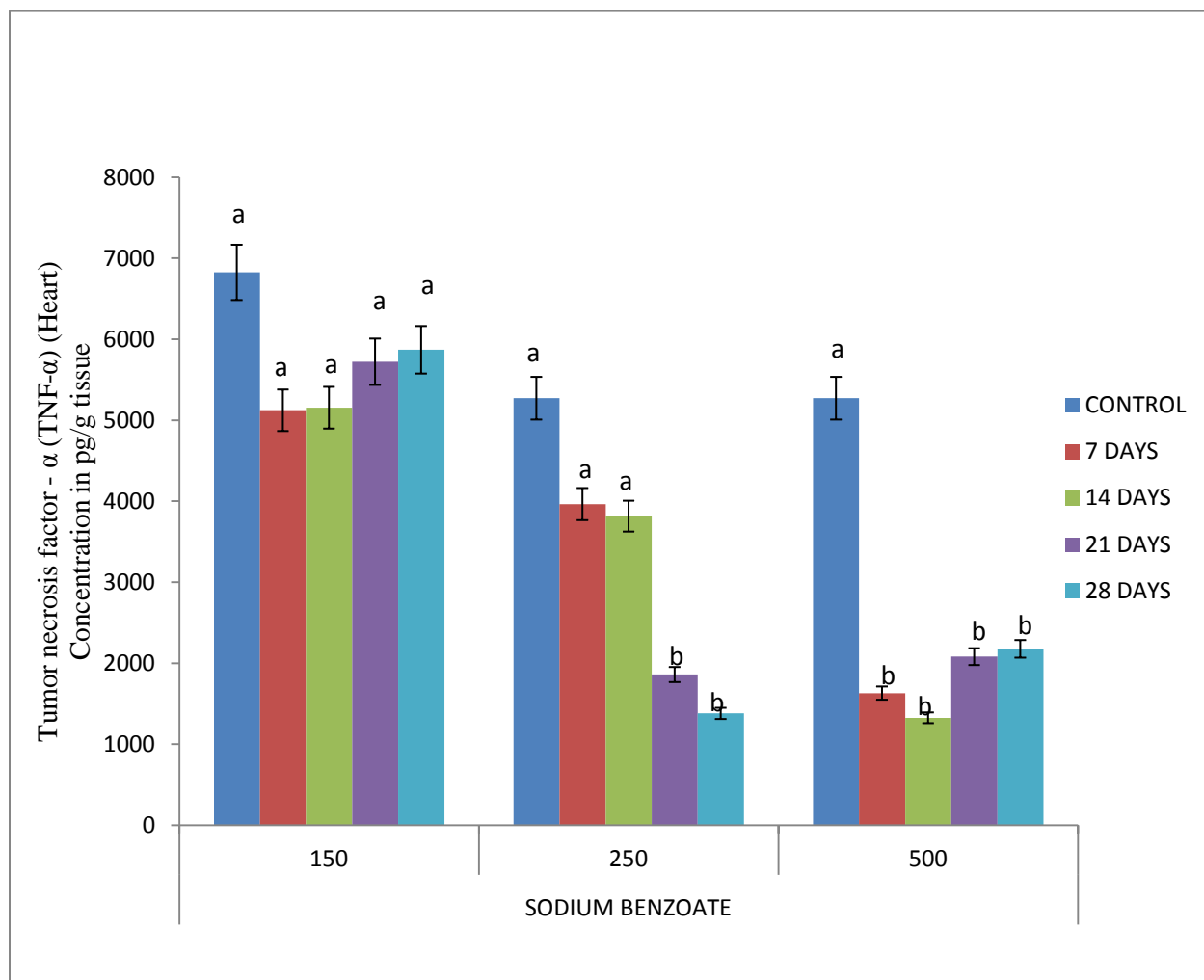
126 For the proinflammatory cytokines of experimental animals in group 2, 3, 4 and 5, tumor
 127 necrosis factor- α and interleukin-6 showed significant decrease in the heart tissue at group 4 and

128 5 of 250mg/kg and group 2, 3, 4 and 5 of 500mg/kg body wt. Values were all compared to the
129 control.



130
131 Fig 2: Effects of varying concentrations of sodium benzoate on interleukin-6 (IL-6) levels in
132 heart tissue.

133 Values are means \pm Standard Error Mean (SEM). Values with different superscript are
134 statistically significant at ($p \leq 0.05$). Superscript (a,b) compares 7 Days, 14 Days, 21 Days and 28
135 Days to control.



137

138 Fig 3: Effects of varying concentrations of sodium benzoate on tumor necrosis factor (TNF)
 139 levels in heart tissue.

140 Values are means \pm Standard Error Mean (SEM). Values with different superscript are
 141 statistically significant at ($p \leq 0.05$). Superscript (a,b) compares 7 Days, 14 Days, 21 Days and 28
 142 Days to control.

143

144

145 **DISCUSSION**

146 The total body content of cholesterol depends on the balance between the amount of cholesterol
147 formed in the body plus that absorbed from diet. Intestinal cholesterol absorption represents
148 another major route for the entry of cholesterol into the body, and, thus, this source can influence
149 the plasma LDL-cholesterol concentration. The cholesterol pool in the intestine comes from
150 dietary cholesterol and the majority from biliary excretion [16]. The deviation from normal
151 values of cholesterol, may be an indication of a change in the cholesterol biosynthesis pathway
152 [17]. This study revealed that cholesterol showed a significant ($p \leq 0.05$) decrease in levels,
153 indicating an effect on lipid mobilization, storage processes, membrane structure and function.
154 Alterations in the concentration of cholesterol can give useful information on the lipid
155 metabolism as well as predisposition of the animals to atherosclerosis and its associated coronary
156 heart diseases [18]. From this study it is seen that sodium benzoate suppressed the mevalonate
157 pathway thereby lowering cholesterol synthesis leading to the depletion of intermediates in the
158 cholesterol biosynthetic pathway as well as lowering cytokine expression. Sodium benzoate is
159 first metabolized by conversion to benzoyl CoA by butyrate CoA ligase, then benzoyl CoA
160 conjugates with glycine-N- acyltransferase to form hippurate. The benzoyl CoA formed inhibits
161 the rate limiting enzyme (3-hydroxy-3-methylglutaryl CoA reductase) leading to the depletion of
162 intermediates in the cholesterol biosynthetic pathway [19]. An earlier study, demonstrated that
163 sodium benzoate is capable of reducing the level of cholesterol in vivo in mice at a level
164 comparable to pravastatin [10], suggesting that the preservative attenuates the cholesterol
165 biosynthesis pathway. This result is similar to that of the present study. Sodium benzoate is seen
166 to behave in a similar way with the statin drug family in their cholesterol lowering effect by
167 inhibiting HMG-CoA reductase as well as specific prenylated proteins. Intermediates of the

168 cholesterol biosynthesis pathway are key regulators of isoprenylation of small G proteins like
169 p21^{ras} and p21^{rac} [20]. Isoprenoids (farnesyl pyrophosphate and geranylgeranyl pyrophosphate)
170 are important attachments for the post-translational modification of a multitude of proteins
171 involved in intracellular signal transduction pathways, including small GTP-binding proteins,
172 which play crucial roles in the regulation of cell growth and differentiation, gene expression,
173 cytoskeletal assembly and cell motility, protein and lipid trafficking, nuclear transport, and host
174 defense [21, 22]. Whereas geranylgeranylation is required for activation of most of the small
175 GTP-binding proteins (e.g. Rho, Rac, Rab, Rap), only few are farnesylated (e.g. Ras) [21].
176 Prenylation of protein (the GTP-bound protein family eg. Ras) by farnesyl pyrophosphate and
177 geranylgeranyl pyrophosphate as substrates activates several downstream signaling pathway that
178 lead to activation of neutral factor kappa b that plays a role in expression of proinflammatory
179 molecules [20]. The Ras proto-oncogene proteins, a family of GTP-binding proteins, function by
180 binding to the cytoplasmic surface of the plasma membrane. This membrane localization of
181 p21^{ras} involves prenylation of cysteine in a CAAX motif present at the C terminus, proteolytic
182 removal of AAX tripeptide, and then carboxymethylation of the C-terminal cysteine [23]. The
183 activation of p21^{ras} by receptor tyrosine kinase occurs through conversion of the GDP-bound
184 inactive form to the GTP-bound active form by Sos and Grb2 and then transduction of signal to
185 downstream effector molecules [24]. The GTP-bound form is converted to the inactive form by
186 the intrinsic GTPase activity, which is accelerated by GTPase-activating proteins [20]. Sodium
187 benzoate (NaB) preferentially attenuates farnesylation of p21^{ras} and thereby inhibits the signal
188 transmission to the downstream signaling molecules [25, 26]. One such downstream candidate is
189 Raf-1 (serine-threonine kinase). The p21^{ras} interacts directly with Raf-1 and is believed to
190 function by positioning Raf-1 at the plasma membrane in the vicinity of its activator, and

191 tyrosine phosphorylation of Raf-1 seems to be essential for p21^{ras}- induced activation of Raf-1
192 [25, 26]. Raf-1, in turn, phosphorylates and activates MEKs and ERKs (members of the MAPK
193 cascade). Therefore, the observed inhibition of cytokine expression may be due to inhibition of
194 NF- κ B activation by NaB due to decrease and/or lack of signal transmission from receptor
195 tyrosine kinase to Raf/MAPK cascade via p21^{ras}. Proinflammatory molecules have been
196 implicated in the pathogenesis of cardiovascular diseases [27]. Transcription factors such as NF-
197 κ B, C/EBP β , AP-1, STAT, IRF-1, etc., play a role in the expression of various proinflammatory
198 molecules, activation of NF- κ B seems essential for the transcription of most of the
199 proinflammatory molecules [28, 29, 30, 31, 32, 33]. Therefore, for a drug to exhibit an anti-
200 inflammatory effect, it is almost mandatory to attenuate the activation of NF- κ B. Importantly,
201 inflammation was shown to be a prominent hallmark of ventricular hypertrophy [34, 35].
202 Interstitial inflammatory cell infiltration involving macrophages, T-lymphocytes, fibrosis, high
203 expression levels of cytokines such as interleukins (IL)-6, IL-1 β , IL-1RA, and tumor necrosis
204 factor-alpha (TNF- α), and activation of inflammatory signaling pathways such as nuclear factor
205 kappa B (NF- κ B) are all characteristic hallmarks of a pathologically hypertrophied heart [36,
206 37]. The pathogenic role inflammation plays is not clearly understood; however, it most probably
207 exacerbates the disease condition. For example, IL-6 was shown to directly induce hypertrophy
208 both *in vitro* and *in vivo* [38, 39]. Furthermore, macrophage microRNA-155, induced by pro-
209 inflammatory stimuli, including lipopolysaccharide (LPS), TNF- α , and interferon-gamma (INF-
210 γ), promotes cardiac hypertrophy and failure [27]. Additionally, targeting inflammatory cell
211 receptors and mediators was shown to modify the disease process and might preserve cardiac
212 function [40, 41].

213

214 **CONCLUSION**

215 The experimental findings at these concentrations of sodium benzoate, reflects its effect on
216 cholesterol, and proinflammatory cytokines; suggesting modulation of the inflammatory pathway
217 due to its administration. This highlights a novel anti-inflammatory role via modulation of the
218 mevalonate pathway and p21^{ras}.

219

220 **COMPETING INTERESTS**

221 Authors have declared no competing interest exist.

222

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