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Ascorbic acid interaction with phytol: a modulatory effects on the anti-pyretic activity of paracetamol in Swiss albino mice

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Abstract

Background: Antioxidants have protective capacity, and can be used combinedly with other substances. Both, ascorbic acid (AA) and phytol (PHY) have many important biological activities, including antioxidant, anti-inflammatory, and organ protective activity. Recently, PHY has been found to exert an anti-pyretic effect in a mouse model. This study aims to evaluate the combined effects of AA and/or PHY with paracetamol (PARA) in Brewer's yeast-induced fever mice model.

Methods: AA (125 mg/kg) and/or PHY (200 mg/kg) were orally co-treated with the PARA (100 mg/kg, p.o.) in Brewer's yeast-induced fever Swiss mice. Data were analyzed by using GraphPadPrism software (version: 6.0), considering $p < 0.05$ at 95% confidence interval, and using one-way analysis of variance (ANOVA) through time, followed by Dunnett's post hoc multiple comparison test.

Results: PARA alone and with PHY and/or AA significantly ($p < 0.05$) reduced rectal temperature at 1st h of observation. PHY reduced rectal temperature at 2nd h, then maintained basal temperature over the observation period (4 h). AA showed an insignificant anti-pyretic effect in experimental animals. However, in combination groups, AA (i.e., with PHY or PARA) did not found to interfere the PHY and PARA mediated reduction of rectal temperature in the animals. Furthermore, AA when co-treated with the PARA + PHY, it caused a slight hypothermic temperature at 1st h, which was then started to reestablish from 2nd to 3rd h, and normalized at 4th h.

Conclusion: Taken together, AA did not interfere anti-pyretic effects of PARA and PHY, suggesting its possible use as a combination substance.

Keywords: *Mus musculus*, Pyrexia, Ascorbic acid, Phytol, Paracetamol

Introduction

Paracetamol (also known as acetaminophen and APAP), a popular medication is used in pain and fever. It is typically used in mild to moderate pain [8, 23] and is often sold in combination with caffeine (augmenting analgesic and antipyretic effects), and other medications, including

psychoactive drugs and cold medications. Paracetamol (PARA) is also used for severe pain, cancer pain and pain after surgery, in combination with opioid pain medications. It has an oral (e.g., tablet, syrup), rectal (e.g., suppository) and injectable dosage forms [29]. Its effects generally last between 2 to 4 h and it is classified as a mild analgesic [29] rather than anti-inflammatory drug [22]. However, its exact mechanism of action is yet to be investigated [22]. Cumulative reports suggest that PARA acts through the cyclooxygenase (COX) pathway [2]. Ghanem et al. [10] suggests that PARA exerts an anti-pyretic effect through inhibiting the COX-2 enzyme. It

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may also inhibit prostaglandin synthesis in the central nervous system (CNS) [2]. However, the PARA-associated damage in the liver and kidney is currently a worldwide problem [4].

Phytol (PHY; 3,7,11,15-tetramethylhexadec-2-en-1-ol), a chlorophyll-derived diterpenoid is in the spotlight due to its diverse biological activities, suggesting a possibility in its biomedical application [17]. It has been seen to exhibit an anti-inflammatory effect through inhibiting neutrophil migration by a reduction in interleukin 1 beta (IL-1 β) and tumor necrosis factor alpha (TNF- α) level and in a recent study, it has been found to exert an anti-pyretic effect in a dose-dependent manner in adult male Wistar rats [15]. In this study, the author suggests, via molecular docking study, that PHY may exert anti-pyretic effects through the 5IKR-dependent COX-2 inhibition pathway. On the other hand, ascorbic acid (AA, also called vitamin C), is a frequently used vitamin in human [19]. AA was initially identified as the factor preventing the scurvy disease, and became very popular for its antioxidant property. Although, the role of AA in prostaglandin synthesis has been yet to disclose [13] but in rabbits, anti-pyretic effect of PARA was potentiated by concomitant administration of this vitamin [6].

Oxidative stress seems to be involved in the toxicity of PARA [31] and the use of antioxidants with it has been found to reduce PARA-induced oxidative damage [12, 24]. Recently, the AA has been identified as an important vitamin that can be used to manage all stressful conditions linked to inflammatory processes and immunity, therefore, it can be considered as a combination component with other substances, including antioxidants and drugs [28]. This study aims to investigate the combined effects of AA and PHY on the standard anti-pyretic drug PARA in Brewer's yeast-induced fever mouse model.

Materials and methods

Reagents and chemicals

Brewer's yeast was purchased from the local market in Gopalganj, Bangladesh. PARA was kindly supplied by the Beximco Pharmaceuticals Ltd., Bangladesh, while the PHY was purchased from the Sigma-Aldrich (Chem Ex. Co. St. Louis, Missouri, USA). AA, tween 80 and NaCl were purchased from the Merck, India.

Experimental animals

Forty adult male albino mice (21–28 g), purchased from the animal resource branch of Jahangir Nagar University (JU), Dhaka, were used for this study. The animals were housed under standard environmental conditions (temperature: 25 \pm 2 $^{\circ}$ C, humidity: 50 \pm 5%, and 12 h light/dark cycles) in sanitized polypropylene cages containing sterile paddy husk as bedding. Animals were freely accessed to standard pellets as basal diet and water

ad libitum. All the animals were acclimatized for 7 days before starting the study. The animals were randomized into experimental and control groups and the food was withdrawn 12 h before the treatment start.

Groups and treatments (Brewer's yeast induced hyperthermia test in mice)

This study was carried out by Brewer's yeast induced fever model described by Tomazetti et al. [30]. Rectal temperature (basal) was recorded of each mouse by using a clinical digital thermometer (MS Digital Thermometer, India). After basal rectal temperature measurement (temperature range 89.5 to 107.5 $^{\circ}$ F), fever was induced by subcutaneous injection of 15% (w/v) suspension of Brewer's yeast in distilled water at a dose 10 mL/kg body weight (bw). Only mice, which rectal temperature increased at least 1 $^{\circ}$ F (0.6 $^{\circ}$ C) after 18 h of Brewer's yeast injection were selected to participate in the study (this temperature measurement was called 0 h). Selected animals were randomly divided into eight groups ($n = 5$, each group); treatment details have been shown in Table 1. PARA and PHY doses had been tested in a previous study [15]. After the treatment of samples/controls, rectal temperature of each mouse was recorded at 1, 2, 3 and 4th hour.

Statistical analysis

All values are expressed as the mean \pm standard error of the mean (SEM) and the results were analyzed statistically by one-way analysis of variance (ANOVA) through time, followed by Dunnett's post hoc multiple comparison test by using GraphPadPrism software (version: 6.0, San Diego, California, USA. copyright© 1994–1999), considering $p < 0.05$ at 95% confidence interval.

Results

Table 2 suggests that oral administration of PARA 100 mg/kg (bw) significantly ($p < 0.05$) reduced rectal temperature at 1st h and it maintained basal temperature during the observation period in animals. PHY at 200 mg/kg (bw) reduced rectal temperature at 2nd h, then it also maintained basal temperature over the observation period. No significant reduction of rectal temperature was seen in AA (125 mg/kg) group until 3rd h of observation. At 4th h AA was found to decrease the temperature slightly in the animals. However, AA in combination groups (AA + PHY and AA + PARA) did not interfere the PHY and PARA mediated reduction of rectal temperature in animals. Moreover, AA when co-treated with the PARA and PHY, it attained a slight hypothermic temperature at 1st h, and the basal temperature was then normalized at 4th h.

Table 1 Animals fasting overnight are treated with the following substances at 10 mL/kg

Treatment groups	Description
Brewer's yeast subcutaneous injection	15% w/v suspension
Gr-I: VEH (p.o.)	10 mL/kg bw (0.05% Tween 80 dissolved in 0.9% NaCl solution)
Gr-II: PARA (p.o.)	100 mg/kg (dissolved in VEH)
Gr-III: PHY (p.o.)	200 mg/kg (emulsified in VEH)
Gr-IV: AA (p.o.)	125 mg/kg (emulsified in VEH)
Gr-V: PHY + AA (p.o.)	Gr-V to Gr-VIII PARA are administered after 15 min of PHY and/or AA administration
Gr-VI: PHY + PARA (p.o.)	
Gr-VII: AA + PARA (p.o.)	
Gr-VIII: PHY + AA + PARA (p.o.)	

AA ascorbic acid, bw body weight, PARA paracetamol, PHY phytol, p.o. per-oral, VEH vehicle

Discussion

The Brewer's yeast suspension induced pyrexia model is more commonly used to study the anti-pyretic potential of a wide variety of substances, including crude extracts or their derivatives, chemicals or drugs. In this model, pyrexia is produced due to an enhanced formation of proinflammatory mediators like IL-1 β and TNF- α , from the infected or damaged tissue(s), which stimulate synthesis of prostaglandin E2 (PG-E2) near preoptic hypothalamus area and triggers to rise body temperature [9, 22]. Natural products are used as a traditional tool for the treatment of various diseases [16].

PARA is commonly used to treat pain (mainly pain associated with osteoarthritis) and fever, especially of choice in patients that cannot be treated with non-steroidal anti-inflammatory drugs (NSAIDs), such as people with bronchial asthma, peptic ulcer disease,

hemophilia, salicylate-sensitized people, children under 12 years of age, pregnant or breastfeeding women [5, 18]. The mechanism of action of PARA is complex that includes the effects of both the peripheral (COX inhibition), and central (COX, serotonergic descending neuronal pathway, L-arginine/nitric oxide (NO) pathway, cannabinoid system) pathways. Although, PARA is well tolerated drug it produces some side effects in the gastrointestinal tract and hepatic system [18], thus its safety has questioned the validity of the sale of this drug without being a prescription [7]. In a PARA overdose situation, the metabolism of this drug (glucuronidation and sulfuration in the liver) is saturated and subsequently metabolized to N-acetyl-p-benzoquinone imine (NAPQI) by cytochrome P450 [2]. NAPQI is a toxic substance which is safely reduced by glutathione (GSH) to nontoxic substance. A PARA overdose depletes the GSH

Table 2 Anti-pyretic effects of phytol and/or ascorbic acid and controls in Brewer's yeast-induced pyrexia in mice

Treatment	Rectal temperature (°F)					
	Basal [#]	0 h (after 18 h ^{##})	1 h ^{###}	2 h ^{###}	3 h ^{###}	4 h ^{###}
Gr-I: Control (n = 5)	98.50 \pm 0.18	100.67 \pm 0.23	100.77 \pm 0.14	100.73 \pm 0.09	100.63 \pm 0.18	100.58 \pm 0.27
Gr-II: PARA (n = 5)	98.46 \pm 0.09	100.40 \pm 0.09	98.47 \pm 0.23 ^{*a,c}	99.37 \pm 0.12 ^{*a}	98.41 \pm 0.31 ^{*a}	98.46 \pm 0.37 ^{*a}
Gr-III: PHY (n = 5)	98.48 \pm 0.11	100.48 \pm 0.17	99.58 \pm 0.09 ^a	98.48 \pm 0.23 ^{*a}	98.38 \pm 0.12 ^{*a}	98.44 \pm 0.09 ^{*a}
Gr-IV: AA (n = 5)	97.27 \pm 1.45	97.93 \pm 1.49	98.07 \pm 1.43 ^a	98.04 \pm 1.11 ^a	97.93 \pm 0.11 ^a	97.83 \pm 0.47 ^a
Gr-V: PHY + AA (n = 5)	96.30 \pm 0.58	97.37 \pm 0.33	97.73 \pm 0.69 ^{*a,c}	96.33 \pm 1.16 ^{*abcd}	96.22 \pm 0.49 ^{*abcd}	97.31 \pm 0.35 ^{abc}
Gr-VI: PHY + PARA (n = 5)	98.46 \pm 0.16	100.50 \pm 0.11	98.47 \pm 0.09 ^{*a,c}	98.45 \pm 0.06 ^{*a}	98.42 \pm 0.09 ^{*a}	98.47 \pm 0.14 ^{*a}
Gr-VII: AA + PARA (n = 5)	99.30 \pm 0.35	99.90 \pm 0.26	99.33 \pm 0.35 ^a	99.26 \pm 0.18 ^a	99.33 \pm 0.15 ^a	99.29 \pm 0.20 ^a
Gr-VIII: PHY + AA + PARA (n = 5)	99.93 \pm 0.76	100.63 \pm 0.22	99.83 \pm 0.59 ^a	99.85 \pm 1.22 ^a	99.89 \pm 1.04 ^a	99.92 \pm 1.51 ^a

[#]Rectal temperature before fever induction, ^{##}Rectal temperature after 18 h of fever induction, ^{###}Time after treatment

AA ascorbic acid, PARA paracetamol, PHY phytol. Values are mean \pm SEM. Statistical analysis: ANOVA followed by Dunnett's multiple comparisons $p < 0.05$ when compared to *0 h (respective group); ^acontrol, ^bPARA, ^cPHY, ^dAA

Gr-I: Control (vehicle)

Gr-II: PARA (100 mg/kg)

Gr-III: PHY (200 mg/kg)

Gr-IV: AA (125 mg/kg)

Gr-V: PHY (200 mg/kg) + AA (125 mg/kg)

Gr-VI: PHY (200 mg/kg) + PARA (100 mg/kg)

Gr-VII: AA (125 mg/kg) + PARA (100 mg/kg)

Gr-VIII: PHY (200 mg/kg) + AA (125 mg/kg) + PARA (100 mg/kg)

stores, and once they reach less than 30% of normal, NAPQI levels increase and subsequently binds to hepatic macromolecules causing irreversible hepatic necrosis [11]. The reduction/restoration of oxidized glutathione (GSSG) is a crucial point to avoid PARA toxicity. AA restores GSH levels [27, 33] and may decrease PARA toxicity without decreasing its anti-pyretic effects.

It is evident that PARA's overdose can cause severe liver injury, liver necrosis and kidney damage in human beings and animals [4]. Overproduction of reactive oxygen and nitrogen species (ROS/RNS), and oxidative stress in such organs seems to be involved in PARA toxicity [31]. Antioxidants can be used as combination substances with PARA therapy, especially those having no antagonizing effects [26]. To date, a number of antioxidant molecules have been reported to counteract PARA-induced oxidative damages. Apigenin (10 mg/kg bw for 6 days) inhibited lipid peroxidation and increased the enzymatic antioxidant defense mechanisms in PARA-induced hepatotoxicity in rats [26]. In adult male albino rats, curcumin pretreatment (100 mg/kg bw for 7 days) prevented the toxic effects of PARA and inhibited the elevation of the total oxidant status and oxidant status index [3]. In mice, ginsenoside Rk1 (10 and 20 mg/kg bw for 7 days) ameliorates PARA-induced hepatotoxicity via antioxidant, anti-inflammation, antinitrative, and antiapoptosis mechanisms [14]. In a recent study, AA (500 mg/kg bw for 8 days) has been found to protect PARA-induced oxidative liver damage in rats [1]. In another study, AA (100 mg/kg bw for 3 days) amplified the antioxidant defense potential and exhibited a strong hematoprotective effect against PARA-induced damaging effects in rats, suggesting a promising co-therapeutic option with this drug [21]. In this study, AA did not interfere anti-pyretic effects of PARA.

Cumulative evidence suggests that diterpenes are protective in nature and can be used to protect oxidative damage caused by PARA [34]. In some studies, it has been suggested that diterpenes have the painkiller capacity [25] and can be co-treated with PARA to treat many diseases, including cancers [20, 32]. In our study, PHY was found to exert a significant anti-pyretic effect in mice, which is an agreement with the report suggested by Islam [15]. Moreover, PHY did not antagonize PARA-mediated anti-pyretic effect in the experimental animals, neither its activity encountered by AA. Interestingly, PHY when combined with the AA and PARA, it reduced the rectal temperature in experimental animals.

Conclusion

AA did not exhibit anti-pyretic effect in Brewer's yeast-induced fever mice model. PHY reduced rectal temperature at 2nd h and maintained the thermal balance like the basal temperature throughout the

observation period (4 h). AA and/or PHY did not interfere PARA-mediated anti-pyretic effects in the experimental animals. Furthermore, AA and PHY when co-treated with the PARA a significant reduction of rectal temperature was seen in the animals. It may be due to a synergistic effect by the AA and PHY on the anti-pyretic effect of PARA. Further studies are necessary to understand the possible mechanism of action behind this combined anti-pyretic effect. Moreover, new studies are needed to evaluate a possible lower toxicity of these treatments.

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Authors' contributions

MMR- Laboratory work, data collection & writing of primary draft; SMHH - Data collection & writing of primary draft; MM- Final drafting and revision; JSR- Final drafting and revision; MTI- Study design, data manipulation and analysis, writing of the final draft.

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Ethics approval and consent to participate

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Consent for publication

The authors declare their consent for publication.

Competing interests

The authors declare no conflicts of interest.

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