Curcumin Alleviates Potassium Bromate-Induced Hepatic Damage by Repressing CRP Induction through TNF-α and IL-1β and by Suppressing Oxidative Stress

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Abstract

This study evaluated the prospective molecular and biochemical mechanisms behind the hepatoprotective effects of curcumin in Wistar rats exposed to KBrO3. Techniques for assessment of hepatic oxidative injury and histological biomarkers were used. The concentrations of proteins connected with inflammation (e.g. tumor necrosis factor-alpha (TNF-α), interleukins 1β (IL-1β) and C-reactive protein (CRP)) were estimated by enzyme-linked immunosorbent assay (ELISA) techniques. Results showed that, curcumin administered orally at a dose of 20 mg/kg for 28 days significantly suppressed the activities of serum transaminases and alkaline induced by KBrO3 administration (20 mg/kg, twice weekly) and protected the integrity of the liver tissue. Also, curcumin at the tested dose abridged the KBrO3-induced increase in hepatic malondialdehyde (MDA) levels and reversed KBrO3-mediated reduction in activities of hepatic antioxidant molecules including reduced glutathione (GSH), total thiol (TSH), glutathione peroxidase (GPx), catalase and superoxide dismutase (SOD). In addition, curcumin significantly assuaged inflammatory response in KBrO3-lesioned liver as revealed by the decrease in inflammatory biomarkers. This study suggests that curcumin exhibits a protective effect via induction of hepatic detoxification proteins and inhibition of inflammatory proteins in addition to its antioxidative ability in KBrO3-induced hepatic injury in rats.

Keywords: C-reactive protein; curcumin; cytokines; hepatoprotective; potassium bromate

Introduction

Potassium bromate (KBrO3) is required for a wide range of activities in many industries such as food and cosmetics industries (IARC, 1986). However, exposure to unwarranted level of potassium bromate via, for instance, food can induce hepatic damage among other organ damage including neurotoxicity, and tumor induction in experimental animals or renal carcinomas induction in animals and humans (De Angelo et al., 1998; Zhang et al., 2010). The mechanisms of KBrO3-induced hepatotoxicity have been identified to involve oxidative stress among others (Chipman et al., 1998; Umemura et al., 1998; Murata et al., 2001; Li et al., 2015; Tsuchiyah et al., 2018). KBrO3 results in significant reduction in the levels and activities of non-enzymatic and enzymatic antioxidant molecules including reduced glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase in the liver and many other organs (Khan et al., 2012; Sahreen et al., 2013; Tsuchiya et al., 2018). The involvement of reactive oxygen species (ROS) such as H2O2, hydroxyl radicals (OH·) and superoxide anion (O2-) in KBrO3-induced hepatotoxicity has been reported thereby culminating in oxidative stress, which is one of the important mechanisms for several pathological conditions including hepatic injury, tissue wasting, neoplastic transformation, and tumor generation (Nakae et al., 1997; Wills et al., 2006; Pradeep et al., 2007; Uchida et al., 2018).

Hepatocytes are known to constantly secrete vast array of proteins which serve crucial functions in the activation of innate immunity (Zhou et al., 2016), and these proteins are categorized as acute-phase proteins (APPs). The production of these APPs are enhanced by many inflammatory cytokines, including Interleukin 1 beta (IL-1β), and tumor...
necrosis factor- alpha (TNF-α) (Zhou et al., 2016). These inflammatory cytokines have been reported to be early mediators connected to tissue damage and repair, and that high level of IL-1β is connected to liver damage while TNF-α may also be induced in hepatic damage (DeCicco et al., 1998). C-reactive protein (CRP) is one of the acute-proteins that is critically involved in inflammatory responses, it is generally employed as a biomarker to identify acute and chronic inflammation (Wang and Sun, 2009). Improper elevation of CRP has been frequently observed in some malignancies including hepatocellular (Wang and Sun, 2009). Like some other gene products, the secretion of CRP in hepatocytes is predominantly induced at the transcriptional level and the level can be enhanced by proinflammatory mediators including IL-1β and TNF-α (Castell et al., 1990; Wang and Sun, 2009). Elevated CRP has been observed in patients with different cancer types and has been suggested to be a secondary response to tumor necrosis, local tissue damage, and associated inflammation in cancer patients (De Mello et al., 1983; Falconer et al., 1995; Gockel et al., 2006; Crumley et al., 2006). Since various studies have demonstrated the correlation of elevated CRP levels with incidence of malignancies, agents with CRP-lowering capacity are being considered to be potentially effective in cancer prevention and therapy (Wang and Sun, 2009). Other attempts have targeted the inducers of CRP i.e. the cytokines (e.g. IL-1β, and TNF alpha) to indirectly suppress CRP in cancers and diseases associated with inflammation (Wang and Sun, 2009). A number of agents (COX inhibitors and lipid-lowering agents) have provided promising results in lowering serum levels of CRP in cancer therapy (Kennon et al., 2001; Zimmerman et al., 2003; Nissen et al., 2005; Prasad, 2006). Vast array of dietary active compounds have also been demonstrated for their anti-inflammatory and anticarcinogenic activities (First and Zündorf, 2014; Griffiths et al., 2016). However, assessment of their capacity to regulate serum level of CRP and the inflammatory cytokines will provide an insight to the molecular mechanism behind their anti-inflammatory activities.

For centuries, Curcuma longa L. (Turmeric) rhizomes, a member of the Zingiberaceae family, has been broadly employed as the indigenous medicinal plant especially for the management of diseases associated with inflammation (Ammon and Wahl, 1991). Among the active components of Tumeric, curcumin happens to be the most important, and a vast array of biological and medicinal activities such as antioxidative, anticarcinogenic, antimicrobial, antifungal and anti-inflammatory activities to mention a few have been attributed to curcumin (Araujo and Leon, 2001; Maheshwari et al., 2006). Many studies have revealed the curative effects of curcumin against hepatotoxicity and oxidative stress induced by cadmium (Mohajeri et al., 2017), dimethylisothiazoline (Kyung et al., 2018), Thioacetamide (Elmans et al., 2017), propanil (Ottechere et al., 2014) and cadmium - induced renal toxicity (Akinwumi et al., 2017) in experimental models. Part of its mechanism of action has been reported to be either through direct interaction with molecular targets or alteration of gene expression and signaling pathways (Kyung et al., 2018). Reports on the effectiveness of curcumin in the inhibition of liver cirrhosis through the regulation of many pathways for example, NF-κB pathway and inhibition of oxidative stress has been recently established (Cai et al., 2017). Obaidi et al. (2018) reported the ability of curcumin to suppress the carcinogenic potential of KBrO₃ by reducing the level of H₂O₂ and 8-OHdG DNA adducts (Obaidi et al., 2017). Despite these reports, the molecular mechanisms behind the hepatoprotective activities of curcumin are yet to be fully understood. Here, we account that Curcumin alleviates potassium bromate-induced hepatic damage by repressing CRP induction through TNF-α and IL-1β and by suppressing oxidative stress.

Materials and Methods

Chemicals and reagents

Rat C-reactive protein (CRP) Catalog Number.CSB-E07922r; rat TNF-α Catalog Number. CSB-E11987r and; rat interleukin-1β (IL-1β ) Catalog Number.CSB-E08055r ELIZA kits were supplied by e-Bioscience, Inc. KBrO₃ (CAS NO: 7758), (99% purity) was supplied by Lab-Tech Chemicals. Curcumin, Glutathione (GSH), 5,5’-dithiobis-2-nitrobenzene (DTNB), 2-thiobarbituric acid (TBA), Biuret and 1 chloro-2, 4-dinitrobenzene (CDNB) and hydrogen peroxide (H₂O₂) were manufactured by Sigma-Aldrich, St Louis, MO, USA. All other reagents and chemicals used in this study were of analytical grade and water used was glass distilled.

Experimental animals

The animals used for this study were thirty (30) male rats of Wistar strain, weighing about 160–210 g and they were obtained from the Central Animal House, College of Health Sciences, Osun State University, Osogbo. These were acclimatized for 7 days in plastic cages in the animal house at an ambient temperature of 25 °C and a relative humidity of 45-55%, with 12 hours each of dark and light cycles. Animals were sustained on normal laboratory chow and fresh water ad libitum. The handling and use of the animals were in accordance with NIH Guide for the care and use of laboratory animals.

Treatment groups/study design

Animals were distributed into 5 experimental groups (n = 6). Saline/vehicle, which is negative control group received oral administration of 0.8% saline daily, olive oil/vehicle control group received oral administration of olive oil daily. Olive oil/curcumin group received daily oral administration of olive oil containing 20 mg/kg/bodyweight of curcumin, KBrO₃/vehicle, which is positive control group received oral administration of 0.8% saline containing 20 mg/kg/bodyweight KBrO₃ twice a week, KBrO₃/curcumin combination group received daily dose of curcumin and dose of KBrO₃ twice a week. In the present study, potassium bromate was orally administered to rats as described by (Khan et al., 2012) and the dosage of KBrO₃ was chosen according to previous report (Bayomy et al., 2016) where it induced hepatic functional alterations, while the choice of the curcumin dosage was made based on the acceptable range reported for daily intake (NCl, 1996). KBrO₃ was diluted in saline and the curcumin in olive oil;
both solutions were prepared freshly and administered (1 mL/kg). Curcumin was administered daily while KBrO₃ was administered twice weekly and two hours after curcumin. The experiment lasted for a period of 28 days, after which animals werefasted overnight and sacrificed 24 hours after the last dose under light ether anesthesia. Blood samples were obtained by heart puncture and centrifuged at 3000g for 10 minutes. The clear non-hemolyzed sera were stored at -20°C till subsequent measurements.

Tissue collection and preparation

The livers were quickly expelled and rinsed in cold 1.15% KCl solution, blotted on filter papers to remove adhering blood, and homogenized in 100 mM potassium phosphate buffer, pH 7.5. The homogenates were centrifuged at 10,000 g for 20 minutes at 4 °C, and the supernatant was used for subsequent biochemical assays. A fraction was fixed in 10% neutral buffered formalin solution for histological examination.

Determination of serum hepatic function biomarkers

The hepatic function biomarkers Alanine amino transferases (ALT) and Aspartate amino transferases (AST) activities were determined following the principle reported (Reitman and Frankel, 1957). Alkaline phosphatases (ALP) activity was determined following the method described by Englehardt (1970). Total protein concentrations of the serum were determined according to Biuret method as described by Gornall et al. (1949). Albumin concentration was determined following the principle reported by Grant (1987).

Estimation of antioxidant status

Catalase (CAT) activity was measured using hydrogen peroxide as the substrate according to the method previously described (Manubolu et al., 2014). Superoxide dismutase (SOD) activity was determined by measuring the inhibition of autoxidation of epinephrine at pH 10.2 and 30 °C according to Misra and Fridovich (1972). Reduced glutathione (GSH) was determined according to the method of Jollow et al. (1974). Activity of Glutathione peroxidase (GPx) was estimated following the method reported by Rotruck et al. (1973) while Total thiol (TSH) content in the liver homogenate was determined as described by Ellman (1959).

Lipid peroxidation

Lipid peroxidation was determined as the formation of thiobarbituric acid reactive substances during an acid-heating reaction, according to Ohkawa et al. (1979). Briefly, the reaction mixture consisting of 200 µL of kidney homogenates or standard [0.03mM malondialdehyde (MDA)], 200 µL of 8.1% sodium dodecyl sulfate, 500 µL of 0.8% thiobarbituric acid, and 500 µL of acetic acid solution (2.5M HCl, pH 3.4) was heated at 95 °C for 1 hour. The absorbance was measured at 532 nm. Tissue levels of thiobarbituric acid reactive substances were expressed as mmol MDA/mg of protein.

Assay of serum C-reactive protein, IL-1β and TNF-α

Enzyme-linked immunosorbent assay: rat C-reactive protein (CRP); rat TNF-α and rat interleukin-1β (IL-1β) ELISA Kits were used to measure the concentrations of high sensitive C-reactive protein (CRP), interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) by following the instructional manual.

Histopathological analysis

The liver tissues were excised from the animals after sacrifice and stored in 10% formalin solution, for tissue sections and subsequent histopathological examination. The tissues were then embedded in paraffin. A rotary microtome was used to collect five micrometre-thick paraffin sections, and tissues were thereafter stained by hematoxylin and eosin (H & E). The specimens were examined and photographed under a light microscope.

Statistical analysis

The data were expressed as mean ± standard deviation (SD) after analysis by one-way analysis of variance (ANOVA) with the aid of Graph Pad Prism version 5. For windows (GraphPad software, San Diego, CA), followed by Post hoc Bonferroni comparative test Differences between mean values of different groups were considered statistically significant at P < 0.05.

Results

Effect of curcumin on the same serum hepatic biomarkers in rats exposed to KBrO₃

The ability of curcumin to alleviate KBrO₃-induced hepatic damage was estimated by determining the activities of AST, ALT and ALP. As shown in Table 1, pre-treatment with curcumin at a dose of 20 mg/kg significantly reduced the activities of AST, ALT and ALP that were secreted into serum as a result of KBrO₃-induced hepatic damage.

Effect of curcumin on serum levels of CRP and inflammatory cytokines in rats exposed to KBrO₃

The results that revealed serum levels of CRP and inflammatory cytokines: IL-1β and TNF-α evaluated by ELISA techniques are presented in Table 2. As shown, in the table, the three proteins were significantly induced subsequent to KBrO₃ administration. However, upon oral co-administration with curcumin for 28 days, the serum levels of these proteins were significantly regulated.

Effect of curcumin on markers affected during oxidative stress in rats exposed to KBrO₃

Induction of oxidative stress has been reported to be associated with KBrO₃-induced hepatic damage in experimental models (Chipman et al., 1998; Umemura et al., 1998; Murata et al., 2001). To corroborate this view, KBrO₃ caused a significant reduction in GSH and TSH levels (Figs. 1 and 2), and activities of catalase, SOD and GPx, in the liver homogenate (Figs. 3, 4 and 5) with simultaneous increase in MDA formation (Fig. 6). The effects of KBrO₃ on these parameters were adjusted by curcumin.
Table 1. Effects of curcumin on some serum hepatic biomarkers in rats exposed to KBrO3

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Olive-oil</th>
<th>Curcumin</th>
<th>KBrO3</th>
<th>Curcumin+KBrO3</th>
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</thead>
<tbody>
<tr>
<td>AST (u/l)</td>
<td>88.33 ± 7.64</td>
<td>85.00 ± 2.00</td>
<td>86.00 ± 4.58</td>
<td>189.00 ± 5.37abc</td>
<td>112.67 ± 11.15ac</td>
</tr>
<tr>
<td>ALT (u/l)</td>
<td>82.33 ± 2.08</td>
<td>80.00 ± 1.00</td>
<td>81.00 ± 7.00</td>
<td>124.33 ± 4.04abc</td>
<td>96.33 ± 5.51a</td>
</tr>
<tr>
<td>ALP (u/l)</td>
<td>26.67 ± 2.08</td>
<td>23.33 ± 3.51</td>
<td>23.67 ± 3.21</td>
<td>69.00 ± 6.55abc</td>
<td>33.00 ± 2.65a</td>
</tr>
</tbody>
</table>

Control = group treated with saline; oliveoil = group treated with oliveoil; curcumin = group treated with oliveoil + 20 mg/kg curcumin only; KBrO3 = group treated with saline + 20 mg/kg KBrO3 only; curcumin + KBrO3 = group treated with 20 mg/kg curcumin + 20 mg/kg KBrO3. AST = Aspartate transaminase; ALT = Alanine transaminase; ALP = Alkaline phosphatase; SD = standard deviation. a values are significantly (p<0.05) different from control, b values are significantly (p<0.05) different from curcumin + KBrO3, c values are significantly (p<0.05) different from curcumin.

Table 2. Effects of curcumin on serum levels of CRP, and IL-1β and TNF-α in rats exposed to KBrO3

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Olive-oil</th>
<th>Curcumin</th>
<th>KBrO3</th>
<th>Curcumin+KBrO3</th>
</tr>
</thead>
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<tr>
<td>CRP (ng/mL)</td>
<td>7.46 ± 0.54</td>
<td>7.10 ± 0.22</td>
<td>6.32 ± 0.97</td>
<td>17.35 ± 1.05abc</td>
<td>11.08 ± 0.98ac</td>
</tr>
<tr>
<td>IL-1β (ng/mL)</td>
<td>76.20 ± 599</td>
<td>77.12 ± 5.55</td>
<td>75.72 ± 5.49</td>
<td>170.17 ± 5.44abc</td>
<td>122.25 ± 12.17ac</td>
</tr>
<tr>
<td>TNF-α (ng/mL)</td>
<td>20.14 ± 1.05</td>
<td>22.31 ± 2.00</td>
<td>20.77 ± 0.63</td>
<td>80.89 ± 2.41abc</td>
<td>44.53 ± 2.35a</td>
</tr>
</tbody>
</table>

Effect of curcumin on total thiol (TSH) levels in KBrO3-induced liver oxidative damage. Data are presented as the mean ± SD (n = 6). * values are significantly (p<0.05) different from control, **values are significantly (p<0.05) different from curcumin + KBrO3, ***values are significantly (p<0.05) different from curcumin. For details, see legend in Table 1.
Effects of curcumin on the liver histology of rats exposed to KBrO₃

Histological examination of liver tissues also supported these results because the liver samples from group treated with KBrO₃ showed severe cholestasis with generally perturbed histomorphology (Fig. 7D) compared with the control and olive-oil liver sections (Fig. 7A and B). In groups treated with curcumin alone and group pre-treated with curcumin before exposure to KBrO₃, the hepatocytes have histomorphology with no pathological alteration (Fig. 7C and E).

Discussion

While anticarcinogenic effects of bioactive components from medicinal plants have been accounted for via various mechanisms (Surh, 2003; Lee et al., 2007; Farombi et al., 2009), research interest is now being drawn on the involvement of signaling molecules mediating the pathways which link inflammation and cancer (Clevers, 2004). As a result, deliberate obstruction of intracellular signaling pathways which mediate inflammatory reaction becomes a critical consideration to successfully build up chemo-
preventive agents which are molecular target-based (Surh et al., 2005; Farombi et al., 2009). CRP, one of the acute phase proteins (APPs) secreted from the hepatocytes is generally up-regulated in many malignancies including those related to the hepatic cells (De Mello et al., 1983; Falconer et al., 1995; Gockel et al., 2006; Crumley et al., 2006), hence, the deliberate inhibition of signaling network (including e.g. IL-1β, and TNF-α) concerned with upregulation of serum CRP level is considered to be effective in the prevention of malignant diseases. To this end, agents with CRP-lowering capacity are being considered to be potentially effective in cancer prevention and therapy (Wang and Sun, 2009) while other attempts have targeted the inducers of CRP i.e. the cytokines (e.g. IL-1β, and TNF-α) to indirectly suppress CRP in cancers and diseases associated with Inflammation (Wang and Sun, 2009). Therefore, evaluation of CRP and inflammatory cytokines (e.g. IL-1β, and TNF-α) remains relevant in monitoring hepatic toxicity and malignancies.

Reports on the antioxidative, antihepatotoxic and anticarcinogenic properties of curcumin in various experimental models abound (Farombi et al., 2009; Otuechere et al., 2014; Mohajeri et al., 2017; Elmansi et al., 2017; Kyung et al., 2018), but reports on the protective effect of curcumin in KBrO3-induced hepatotoxicity is scarce in literature. Obaidi et al. (2018) reported that curcumin was able to abrogate the carcinogenic potential of KBrO3 by reducing the level of H2O2, and 8-OHdG DNA adduct (Obaidi et al., 2017), however, the molecular mechanisms behind curcumin induced antihepatotoxicity especially against KBrO3 is yet to be fully deciphered. Here, we account that Curcumin alleviates potassium bromate-induced hepatic damage by repressing CRP induction through TNF-α and IL-1β by suppressing oxidative stress. The evident reduction in KBrO3-induced increase in the activities of serum enzymes and lipid peroxidation by curcumin in this study corroborates with prior findings on the hepato-protective ability of this natural compound on several hepatotoxicants (Otuechere et al., 2014; Elmansi et al., 2017). The oxidative capacity of KBrO3 has been demonstrated in many organs (Ahmad et al., 2015). KBrO3 is generally known to be an oxidant inducing oxidative damage in several experimental models. Antioxidants which are capable of suppressing the damaging effects of these oxidants get completely overwhelmed and therefore become drastically reduced leading to a condition regarded as oxidative stress (Uchida et al., 2018) It is not surprising that administration of KBrO3 caused significant reduction in both enzymatic and non-enzymatic antioxidant molecules viz: TSH, GSH, GPx, catalase and SOD. This reduction may not be unrelated to the ability of KBrO3 as an oxidant. Antioxidative potential of curcumin is well established (Elmansi et al., 2017; Mohajeri et al., 2017; Kyung et al., 2018). In this study, the combination group that was fortified with curcumin prior to KBrO3 exposure experienced a significant rise all the antioxidant molecules. The fortification of the animals with curcumin may have led to the boosting of the antioxidant status which in turn becomes capable of combating the oxidative ability of KBrO3 in the hepatocytes. The significant increase in lipid peroxidation as evident by high concentration of malonaldehyde (MDA) may be the explanation at least in part for the liver damage observed in this study. The involvement of lipid peroxidation in the damage of cell membrane due to chain reaction is well established (Ayala et al., 2014). The damage caused by increased lipid peroxidation in the liver of the rats treated with KBrO3 may be the cause of the evident histopathological alterations observed in this group, whereas, the antioxidative capacity of curcumin which prevents lipid peroxidation in the combination group cause a significant prevention of liver damage as shown in the histology of the liver in the combination group.

A link between inflammation and cancer has been established since 1863 when the sites of chronic inflammation were suggested to be the origin of cancer (Balkwill and Mantovani, 2001). A significant association with chronic inflammation (whether infectious or non-infectious causes) has been reported in about 25% of all cancer cases (Perwez and Harris, 2007), in which there is significant elevation of inflammatory markers. Serum C-reactive protein (CRP) has been established as a susceptible indicator for inflammatory activities (Wang and Sun, 2009) and it is reported to be generally up-regulated in several malignancies including those associated with hepatic cells (Crumley et al., 2006; Gockel et al., 2006). Similarly, high level of IL-1β and TNF-α (inducers of CRP) have also been reported to be capable of inducing hepatic damage (DeCicco et al., 1998). As a result of this, agents that lower CRP and its inducers are beneficial in cancer therapy. In this study, administration of KBrO3 caused a significant increase in serum CRP and the inflammatory cytokines IL-1β and TNF-α compared with the control. The ability of KBrO3 to dysregulate markers involved in inflammation has earlier been reported (Obaidi et al., 2017), since KBrO3 has been implicated in different neoplastic transformation, and tumor generation (Nakae et al., 1997; Wills et al., 2006; Pradeep et al., 2007; Uchida et al., 2018) and neoplasm is linked with inflammation (Balkwill and Mantovani, 2001), it may be suggested that inflammation is involved in the mechanisms of KBrO3- induced carcinogenicity at least in part. Prior administration of curcumin before KBrO3 administration resulted in the modulation of the increase in these markers. This suggests that curcumin may be a good candidate for lowering CRP, hence, suitable for chemoprevention. Also, taking into account the role of CRP and inflammatory cytokines in toxicity and tumor transformation, the suppression of these markers by curcumin in the KBrO3 group somewhat clarifies the molecular mechanism by which curcumin exhibits it hepato-protective effect in KBrO3- induced hepatic damage and probably hepatic-neoplasm.

Conclusions

The present study revealed that curcumin regulates the activities and levels of some antioxidant molecules and some enzymes involved in hepatic function in rats exposed to KBrO3. The ability of curcumin to inhibit CRP elevation via suppression of the inflammatory cytokines IL-1β and TNF-α was also shown. Therefore, it can be assumed that the mechanism of the hepatoprotective effect of curcumin in KBrO3- induced hepatic damage involves suppression of
CRP induction through TNF-α and IL-1β and inhibition of oxidative stress. The turmeric plant from which curcumin is isolated is generally known for its medicinal values. In view of this study, addition of curcumin to food may be encouraged to prevent food additive related liver injury.

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Conflict of Interest

The authors declare that there are no conflicts of interest related to this article.

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