World Cancer Research Journal WCRJ 2016; 3 (4): e788

NUTRACEUTICAL AGENTS WITH HEPATOPROTECTIVE EFFECTS IN CANCER PATIENTS

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Abstract – *Regardless of huge advances in targeted medicine, there are no completely effective drugs supporting liver function, helping to regenerate hepatic cells, and offering protection of the organ without toxic effect. As a result, it is essential to recognize low toxic therapeutical alternatives for the treatment of liver diseases. The use of some natural medicaments as plants and fruits have played fundamental roles in human health care: different scientific studies have indicated that positive effects on liver protection can be accredited to the presence of phytochemicals. This review has as its objective the collection of data based on a study conducted into some fruits (grapefruit, cranberries, and grapes) and plants, primarily carduus marianus, which are frequently consumed either by humans in a normal diet and/or as supplemental phytopharmacy and have demonstrated hepatoprotective capacity. The review focuses on natural treatments to help liver function during chemotherapy in cancer patients.*

KEYWORDS: *Hepatoprotection, Natural extract, Silymarin, Hepatocarcinoma, Chronic liver disease.*

INTRODUCTION

Various physiological processes and functions, such as metabolism, secretion (i.e. bile), synthesis (i.e. albumin, coagulation factors), lipid and glycogen storage are modulated by the liver. It is able to eliminate endogenous (waste metabolites) and/or exogenous (toxic compounds) materials via fecal and/or urinary ways[1].

Therefore, hepatic diseases are still among the principal warnings to public health and they are a problem worldwide[1]. The term hepatic disease means the damage to cells, tissues, structure, or liver function, and this harm can be caused by biological causes (bacteria, virus, and parasites), and autoimmune diseases (immune hepatitis, primary biliary cirrhosis), or by the action of different chemicals, such as some drugs [elevated dosage of paracetamol (PCM) and antitubercular medicines], toxic compounds [carbon tetrachloride (CCl_4), thioacetamide, dimethylnitrosamine (DMN), *D*-galactosamine/lipopolysaccharide (GalN/LPS)] and unquestionably, high uptake of alcohol[2]. Despite enormous improvements in modern medicine, there are no completely valid drugs that stimulate hepatic function, offer total protection to the organ, or contribute in repairing hepatic cells[3]. Moreover, some drugs can induce adverse or side effects. Thus, it is necessary to detect different pharmaceuticals for the treatment of hepatic diseases, with the intend to make these agents more valid and less toxic.

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The employment of some plants and the consummation of several fruits have resulted to be quite important for the human health care. Approximately 80% of the world's population has used traditional medicine for health care, which is based mainly on plant materials[1,3]. The beneficial effects of employing medicinal plants and the ingestion of fruits could be assigned to the action of chemical compounds or substances called phytochemicals[4].

In the literature, many studies have treated the impact that various phytochemicals have on health. Among the many mentioned examples, there are: (A) the vinca alkaloids (vincristine, vinblastine and vindesine); (B) the betalain pigments (betain and indicaxanthine); (C) the anthocyanins (cranberries); and (D) the resveratrol. All of these plants have generally been studied because of their chemo protective roles against cancer[5]. Both the medicinal plants and the intake of certain fruits have proved different consequences on the living systems. Although there have been many studies evaluating their hepatoprotective potential, the majority of investigations have focused their analysis of the sedative, analgesic, antipyretic, cardioprotective, antibacterial, antiviral, antiprotozoal, and anticarcinogenic capabilities[6].

Moreover, the empirical proof of the employment of natural remedies for treating the liver disorders has a long history, and has become an innovative discipline of study, with the main intent of studying the use of traditional fruits and medicinal plants by a lot of people and the different phytochemicals deriving from these foods. Generally, liver-protective plants and fruits contain a heterogeneity of chemical specimens like phenols, coumarins, lignans, essential oils, monoterpenes, glycosides, alkaloids, carotenoids, flavonoids, organic acids and xanthenes[6].

This review has as its objective the gathering of data analyzing studies conducted in some fruits and plants that are consumed frequently by humans and that have demonstrated hepatoprotective property, and the study of a resin and some phytochemicals obtained from fruits, plants, yeasts, and algae that have been evaluated in different models of hepatotoxicity. For this reason, the authors of this paper have attempted to produce information and bibliographic support to researchers who are exploring compounds with this potentiality and to endorse the advance of new researches in this field.

The name of a CYP450 enzyme indicates its similarity in structure to other CYPs. The CYPs that have an amino acid sequence homology higher than 40% are assembled into families, and those with homology ≥55% are grouped into subfamilies. Thus CYP1, CYP2, and CYP3 represent different families. Subfamilies are indicated by a letter following the family name. In humans, the enzymes accountable for drug metabolism belong to the CYP family's 1-4 and most of the CYP450-catalyzed reactions can be attributed to six main enzymes (CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4/5). CYP enzymes in families 5 or higher are usually causes for processing steroids rather than drug metabolism[7,8].

HEPATOPROTECTIVE NATURAL REMEDIES

Fruits. The grapefruit (scientific name *Citrus paradisi*) is an important member of the genus *Citrus* of the Rutaceae family[9].

Despite the common consumption of the grapefruit as a fresh fruit or in juice, no studies have directly evaluated its shielding effects against the damage induced by hepatotoxic compounds[9]. Naringerin has also renewed natural protein levels in serum and albumin and hepatic malondialdehyde (MDA) levels. Finally, the antifibrinogenic and hepatoprotective effect of naringenin, indicating its use in the cure of hepatic fibrosis has been shown[10].

Considering both the results of the two recently published studies, it has been shown that this flavonoid is a biologically active compound able to significantly reduce the levels of serum ALAT and ASAT, gamma-glutamyl transpeptidase (GGT), thiobarbituric acid-reactive substances (TBARS) tissue, conjugated dienes, lipid hydroperoxides, protein carbonyl content, bilirubin, ALP, lactate dehydrogenase (LDH), and phase I enzymes; it also increases the action of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GRx), glutathione-*S*-transferase (GST), alcohol dehydrogenase (ADH), and aldehyde dehydrogenase (ALDH), as well as the vitamins C and E levels in tissues, and phase II enzymes in rats with ethanol-treated liver damage, with rats not receiving treatment[11,12].

With respect to naringin, the only study showing proof of the hepatoprotective capacity of this flavonoid resulted from the investigation of Seo et al[13], who have evaluated the function of a naringin intake in the regulation of lipid and ethanol metabolism in male Sprague-Dawley rats. Naringin supplementation has significantly enlarged high-density lipoprotein-c (HDL-cholesterol) and HDL-c/TC ratio, although reducing it among the ethanol-treated groups. Hepatic lipid

TABLE 1. Nutraceutic agents and parameters for efficacy in liver detoxification.

Agents	*Standard dosage (active agents)*	*Parameters for efficacy measure*	*Targets*	*Annotatiom*
Citrus paradisi	(naringenin)	ALAT, ASAT, GGT, TBARS, bilirubin, ALP, LDH, SOD, CAT, GPx, GRx, GST, ADH, ALDH	Antioxidant activities	Ethanol-induced hepatic damage
Vitis vinifera	15%GS; 5 g/kg (resveratrol)	ASAT, ALAT, GGT, LDH, GSH, GRx, SOD, GST, GPx, MDA	Antioxidant activities	Ethanol-induced hepatic damage
Opuntia ficus-indica cladodes (CCE)		ALAT, ASAT, ALP, LDH, albumin		CPF-induced hepatic damage
Chamomile recutita capitula		Serum marker enzymes, bilirubin, glycogen, TBARS assay	Membrane function activity	PCM-induced hepatic damage
Matricaria chamimilla L.	50, 100, 200 mg/kg	ASAT, ALAT, MDA, SOD, GSH, GPx, CAT	Antioxidant activities	CCl4-induced hepatic damage
Silybum marium	25 mg/kg/day	ALAT, ASAT, ALP	Antioxidant activities, stimulating cell regeneration, cell membrane stabilization	CCl_4-induced hepatic damage
Silybum marium-Ginkgo biloba		ALAT, ASAT, GGT, VEGF, MDA, GSH, SOD, GPx, GRx, Commet assay		NDEA-induced hepat-carcinogenesis
Spirulina platensis	100 µg/kg/bw/day (carotenoids)	GOT, GPT, ALP, total albumin, total protein		CCl4-induced hepatic damage
Spirulina lonar		TBARS, SOD, CAT GPx, GST, ASAT, ALAT	Antioxidant activities	PCM-induced hepatic damage
Cuban propolis	25, 50, 100 mg/kg/bw (95% ethanol extract)	ALAT, GSH		PCM-induced hepatic damage
Cuban red propolis	5, 10, 25 mg/kg or 25, 50, 100 mg/kg bw (95% ethanol extract)	ALAT, ASAT MDA		Alcohol-; CCl4-induced hepatic damage
Brazilian propolis	100, 200 mg/kg	GOT, GPT, LDH		D-Ga1N/LPS-; CCl4- induced hepatic damage
Propolis	10 mg/kg (ethanol extract)	GOT, GPT, TGs		Alchol-induced hepatic damage
B-glucan	500, 1000, 2000 mg/kg in 3 doses (paramylon)	GPT, GOT, SOD, CAT		CCl4-induced hepatic damage

accumulation was also notably abridged in the groups treated with naringin in comparison with the group naringin-free among ethanol-treated groups, while no differences have been seen in the pair-fed groups.

Among the Vaccinium, Blueberries/cranberries are not only assimilated in their fresh and/or frozen forms, but they are also present in processed products, such as canned fruits, yogurts, beverages, jams, and jellies. Oxidative stress (OS) and disorder of cellular immunity are useful estimations of the pathogenesis of hepatic diseases caused by diverse xenobiotics [14].

The grape (scientific name *Vitis vinifera*) is renowned for laxative, astringent, diuretic, cicatrizing, immunological stimulant, anti-inflam-

matory, and hypocholesterolemic characteristics, and for the preventive activity against cardiovascular disease and some cancers (mainly prostate and colon)[15,16].

The grape contains a high amount of flavonoids, such as catechins, anthocyanidins, proanthocyanidins, and resveratrol[15,16]. Among these phytochemicals, the resveratrol has been the one considered the most for its probable hepatoprotective property. In fact, it has been proven resveratrol plies a shielding effect by controlling chronic ethanol intoxication[17] and by lowering the harm caused by hepatocarcinogens, like azoxymethane (AOM)[18].

Hepatoprotective Evidences of Natural Remedies

Nopal (Cactus pear) and tuna (Cactus pear fruit) "Opuntia ficus-indica"

Plants of the genus *Opuntia* are the most frequently found of the Cactaceae family. The fruits of this plant, known as prickly pear fruits, are considered a functional food thanks to their bioactive compounds, like vitamin C and vitamin E, polyphenols, carotenoids, flavonoid (for instance, kaemferol, quercetin, and isorhamnetin), taurine, and pigments[19]. These pigments have shown positive properties in the redox-regulated pathways implicated in cellular growth and inflammation, and no toxic effects have been experienced in humans[20].

Also, they induce fragmentation of the DNA in the liver and chromosomal aberrations in bone marrow cells, amplify the expression of the bcl2 antiapoptotic proteins, and reduce the expression of bax. Additionally, the authors have demonstrated that the therapy with Cactus pryor during or after treatment with B(*a*)P or alfa fetoprotein B1 (AFB1) has completely reduces the oxidative damage induced in all of the markers tested, and have also proved that Cactus has an antigenotoxic effect through the reduction of the damage to the genetic material of the liver and to the bone marrow caused by both toxins[21]. Similarly, other authors have observed that CCE is able to inhibit the toxic effects of B(*a*)P and/or AFB1 by differential modulation of the expression of *p53*, which increases in its associated genes, for instance bax and bcl2. Therefore, the effectiveness in protecting against both carcinogens harm of the cactus cladode extract has been concluded by the scientific group and they also have suggested that *Opuntia ficus-indica* could be taken into consideration as a plant with hepatoprotective capacity[22,23].

Chamomile (Matricaria chamomilla or Chamomilla recutita)

Chamomile (*Matricaria chamomilla* or *Chamomilla recutita*) is an annual plant of the composite family Asteraceae and currently is employed as a diuretic, expectorant, antiseptic, antiphlogistic, febrifuge, sedative, anti-inflammatory, and anticarcinogenic[6].

Just like black or green tea, chamomile tea has demonstrated capability of modulating the action of hepatic cytochrome P_{450} sub CYP1A2[24,25].

Silymarin (Silybum marianum)

St. Mary's thistle or carduus marianus (so called in southern Europe), scientific name *Silybum marianum*, is a Mediterranean region native plant belonging to the Asteraceae family[6,26].

German scientists have studied it since 1960 performing chemical investigations of the milk thistle fruit, separating a crude extract composed of active compounds, called silymarin, with hepatoprotective proprieties. Silybin A, silybin B, isosilybin A, isosilybin B, silychristine A, sylichristine B and silydianine are the main components of silymarin, and they have been found in 1975[6,27].Flavonolignans, i.e., a combination composed of flavonoids and lignin structures are the known chemical constituents of silymarin[6,28].

Carduus marianus is among the most important plants for oral treatment of toxic liver damage, with known mechanisms of action. Silymarin has been used as a protective treatment in acute and chronic liver diseases[6,29]. Suppressing toxin penetration into hepatic cells, increasing SOD activity and the glutathione tissue level, inhibiting lipid peroxidation and enhancing hepatocyte protein synthesis are the many mechanisms of its protective capacities.

The liver protective activity of silymarin can be linked to its antioxidant properties, due to the phenolic nature of its flavonolignans. It also operates by stimulating liver cell regeneration and cell membrane stabilization to avoid agents toxic to the liver from entering hepatocytes[30]. Furthermore, silymarin has been salutary for reducing the chances of developing certain cancers[31]. Regarding cancer prevention, the molecular targets of silymarin are specific proteins involved in apoptosis and cell cycle regulations.

The above-mentioned compounds, with two other relative analogs, provide in extremely minute quantities, have been assessed for antiproliferative/cytotoxic activity against human prostate cancer cell lines. Isosilybin B has shown the most potent activity[6,30]. The isolation of six isomers has provided a preliminary investigation of the structure-activity relationship regarding prostate

cancer prevention. Moreover, Silymarin has repressed ultraviolet A (UVA)-produced oxidative stress, which can cause skin damage. Therefore, the topical application of silymarin might be a helpful strategy against skin cancer [31].

Antioxidant properties of Silymarin, deriving from the phenolic nature of flavonolignans, could be demonstrated by its hepatoprotective capacity. It also stimulates the regeneration of liver cell and the stabilization of cell membrane to prevent agents toxic to the liver from entering hepatocytes[32]. The antifibrotic and anti-inflammatory activity of flavonolignans have been shown[33], thanks to their capability of inhibiting leukotriene production.

We will take into consideration only those investigations in which silymarin combined with other compounds has been analyzed. The first study we analyze has treated the research of silymarin, and misoprostol, or the co-administration of both, against CCl_4-induced hepatic lesion in rats. Misoprostol (MSP) at 10, 100, and 1000 µg/kg, silymarin (25 mg/kg) and the combination of MSP (100 mg/kg) + silymarin (25 mg/kg) have been orally dispensed once daily, together with CCl_4 over 15 d. The authors' results have shown that MSP (at all doses) has demonstrated a significant protection against the hepatotoxic activity of CCl_4 in the rats, observing reductions in levels of serum ALAT of 24.7%, 42.6%, and 49.4%, respect to the control group. MSP at doses of 100 and 1000 mg/kg has decreased ASAT in 28% and 43.6% and ALP in 19.3% and 53.4%, respectively. Silymarin, instead, has reduced ALAT, ASAT, and ALP levels, in 62.7%, 66.1%, and 65.1%, respectively. Differently, co-administrating both compounds, the reductions of 61.4%, 66.1%, and 57.5% in ALAT, ASAT, and ALP levels has been induced.

Treatment with MSP, silymarin, or their combination, has markedly reduced histopathological alterations, depletion of hepatocyte glycogen and DNA content by CCl_4. The image analysis of liver specimens has shown a considerable reduction in liver necrosis, with areas of damage of 32.4%, 24%, and 10.2% after MSP (10, 100, or 1000 mg/kg), of 7.2% after silymarin, and of 10.9% after combination treatment of both compounds, in comparison with the CCl_4 control group (46.7%). These results have indicated that the treatment with MSP and silymarin has protected against CCl_4-induced hepatocellular necrosis. So, the combination of these compounds has demonstrated an important therapeutic potential for decreasing hepatic damage [34].

Another important study is the one performed by Salam et al[35]. They studied the protective effects of a blend of Silybum marianum and Aloe vera (the ACTIValoe N-931 complex) against CCl_4-induced acute hepatotoxicity and liver fibrosis. Acute hepatotoxicity has been caused by an Intraperitoneal injection of CCl_4 (50 µL/kg); an ACTIValoe complex N-931 has been orally administered, at doses of 85, 170, and 340 mg/kg, at 48, 24, and 2 h prior and 6 h after the injection of CCl_4. Hepatic fibrosis has been caused by an *ip* injection of CCl_4 over a period of 8 weeks (0.5 mL/kg, twice weekly), and the mice have been treated once daily with the ACTIValoe N-931 complex at the same doses. Both in acute hepatotoxicity and hepatic fibrosis, serum aminotransferase and lipid peroxidation levels are increased while the hepatic glutathione content is decreased. These changes have been prevented by the ACTIValoe N-931 complex, because it has attenuated the TNF-alpha (tumor necrosis factor-α) levels in nitric oxide synthase, in cyclooxygenase 2 and in the expression of mRNA (messenger RNA involved in acute hepatotoxicity. In antifibrotic testing, tissue inhibitor of metalloprotease-1 mRNA expression has been mitigated by through therapy with the complex. The same, hepatic hydroxyproline content and transforming growth factor-beta 1 levels are decreased. Finally, these results have proposed the hepatoprotective effects of *Aloe vera* and *Silybum marianum* against chronic and acute lesions induced by the organochlorine (OC) compound.

A more recent study has demonstrated that combining *Ginkgo biloba* and *Silybum marianum* could increase chemoprevention against hepatocarcinogenesis induced by *N*-nitrosodiethyl-amine (NDEA, Sigma-Aldrich, St. Louis, MO, USA) through their antioxidant properties and their antigenotoxic and antiangiogenic activity.

Kim et al[36] have evaluated these activates after arranging male Wistar albino rats into six experimental groups: a control lot; a second group with intragastrically administered (ig) NDEA at a 10-mg/kg dose five times weekly over 12 weeks inducing hepatocellular carcinoma (HCC); two groups (3 and 4) pre-treated with silymarin and *Ginkgo biloba*, respectively; and finally, two groups (5 and 6) of post-treated animals with each of the extracts. ALAT, ASAT, GGT and vascular endothelial growth factor (VEGF) have been the parameters investigated in the serum and the ones investigated in hepatic tissue have been MDA, Glutathione S reductase (GSH) SOD, GPx, GRx, and the Comet assay. On finalizing the experiment, the authors have determined that in the NDEA group, the MDA level is high with a subsequent reduction in the GSH level and in the SOD, GPx, and GRx activities. Furthermore, the NDEA group has discovered a significant augmentation in serum ALAT, ASAT, and GGT levels and in the VEGF level. Further-

more, NDEA-administered animals have shown a noticeable increase in Comet assay parameters. These biochemical alterations caused by NDEA are confirmed by histopathological assessment of rat livers intoxicated with NDEA, disclosing obvious cellular damage and well-differentiated HCC. In contrast, the silymarin + NDEA-treated groups (3 and 5) and the *Ginkgo biloba* + NDEA-treated groups (4 and 6) have exhibited a significant reduction in MDA levels and a significant enlargement in GSH content and in SOD, GPx, and GRx activities, in comparison with the NDEA group. Silymarin and/or *Ginkgo biloba* also beneficially have down regulated the increases in serum ALAT, ASAT, and GGT activities and in the VEGF level induced by NDEA. In addition, both extracts have significantly decreased Comet assay parameters and have induced an improvement in liver architecture.

Aller et al[37] observed the result of Silymarin and Vitamin E in patients with non-alcoholic fatty liver disease (NAFLD). The authors have reported the conclusions of a pilot study of 36 patients randomized in two groups: the first group treated with Silymarin plus Vitamin E (2 tablets/day), hypo caloric diet (1520 kcal, 52% of carbohydrates, 25% of lipids and 23% of proteins) and exercise for three months, and the second group treated only with hypo caloric diet. The results of this study are interesting and demonstrate that treatments adopted have improved the hepatic functions. These conclusions have been measured by fatty liver index (FLI), liver accumulation product (LAP) and NAFLD-fibrosis score (FS). They have deduced that Silymarin can be an alternative valid therapeutic option especially as a complementary treatment associated with other therapeutic programs.

Currently, a similar pilot study is ongoing in two Italian health institutions, and the preliminary results are comparable to data from Aller et al[37]. One study is designed in two randomized patient groups: the first group has been treated with a combination of anti-oxidant molecules includes Silymarin 400 mg/day, Vitamin E 12 mg/day, N-acetyl cysteine 600 mg/day, Betaine 600 mg/day and Selenium 81 µg/day (3 tablet/day of Epatil®), hypocaloric diet (1500 kcal, 50% of carbohydrates, 20% of lipids and 25% of proteins) and exercise for three months. The second group has been treated only with hypocaloric diet and exercise for three months[38].

Blue green algae spirulina (Spirulina maxima, Spirulina platensis, and Spirulina fusiformis)

Spirulina is a blue-green microscopic filamentous alga that floats freely. It is an organism with the capacity to store different bioactive molecules such as: (1) proteins (60%-65% dry weight) with essential amino acids; (2) polyunsaturated fatty acids (linoleic acid); (3) vitamins (B_{12} and E); (4) polysaccharides; (5) minerals (Na, K, Ca, Fe, Mn, and Se); and (6) pigments (chlorophyll, c-phycocyanin, allophycocyanin, b-carotene, lutein, and zeaxanthin). Usually, the content of the compounds varies in species-to-species proportions but the phytochemicals that are present always in their biomass are c-phycocyanin (with a content of 12.6% in dry spirulina) and high percentages of dietary zeaxanthin[39].

There is different scientific evidence for its biological effects against health problems. In summary, the results demonstrated that it has antioxidant, anti-inflammatory, hypolipemic, antihypertensive, antidiabetic, antimicrobial, neuroprotective, antianemic, immunostimulant, anticarcinogenic and a hepatoprotector [40-43].

Propolis (bee glue)

Propolis is a resinous substance of natural origin, gathered by bees from diverse parts of plants, shoots, and exudates. It possesses diverse biological activities: antioxidant, anti-inflammatory, antibiotic, and antifungal potential[44]. Moreover, it could prevent cardiac alterations and chronic degenerative diseases, such as diabetes and cancer[45,46].

β-*glucans*

The β-glucans are part of a group of polysaccharides localized in the intermediate layer of the cell wall of yeasts, algae, fungi, and some bacteria and cereals (such as barley and oatmeal)[47,48]. Recently, these polysaccharides have acquired great economic importance due to their immunological activity; moreover, many studies have demonstrated their antiviral, antiparasitic, antifungal, antimicrobial, antioxidant, antigenotoxic, antitumor, antimutagenic, and anticlastogenic potential[48]. Despite b-glucans have shown different therapeutic effects, researches about their hepatoprotective potential have been insufficient because of the novelty of this field[49,50].

CONCLUSIONS

Pharmacogenomics provides a unique approach toward investigating, appreciating, and therapeutically serving the individual cancer patient. Continuous investigation and adaptation of pharmacogenomics with respect to malignancy should likely provide improved risk versus benefit ratios with respect to therapeutic efficacy versus side-effect profiles. This approach could allow

the employment of new natural remedial either to avoid or minimize toxicity [11]. Further, effective re-evaluation of drug design toward the generation of novel and specific therapies focused on enzyme pertaining to malignancy may eventually be personalized and individualized to the patient for maximum efficacy.

This review synthesizes the current evidence for the hepatoprotective effects of some natural remedies against toxic agents that cause liver damage. Finally, these foods and natural compounds could offer alternatives to the pharmacological therapeutic options for the treatment of liver diseases in the 3rd millennium[52]. In general, this article identifies and provides evidence of some phytochemicals with hepatoprotective activity, particularly, the mechanisms of action of silymarin that are related to their antioxidant potential. This issue should promote the search for effective protective agents, which must be studied in pre-clinical and clinical trials to determine their safety and their chemo preventive capacity.

Authors' conflict of interest disclosure:
The authors declare that there are no conflicts of interest regarding the publication of this article.

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