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Review article

Possible potentials of curcumin for pregnancies complicated by intra-uterine growth restriction: role of inflammation, angiogenesis, and oxidative stress

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ABSTRACT

Objectives: So far, various etiologies have been stated for Intra-uterine growth restriction (IUGR) with a wide variety of pathways involved in their pathogenesis. Among these pathways, impaired angiogenesis, inflammation, and oxidative stress are among the most important ones. Curcumin has raised notable attention due to its anti-inflammatory and antioxidant activity in different *in-vitro* studies and clinical trials. The present study aimed to investigate the possible potentials of Curcumin for pregnancies complicated by IUGR through different physiological mechanisms.

Methods: A narrative review study was conducted (Iran; 2020). The implemented Mesh-based keywords were "Curcumin" OR "Turmeric" AND "Therapeutic effect" AND "Side effect" OR "Adverse effect" OR "Teratogenic effect" OR "Teratogenicity" AND "Pregnancy" AND "Intra-uterine growth restriction" OR "Intra-uterine growth retardation" AND "Inflammation" AND "Oxidative stress" AND "Angiogenesis". Cochrane Library, PubMed, Up to date, Scopus, and Google Scholar databases were used as academic search engines.

Results: Reviewing the included studies showed the dual effects of curcumin on angiogenesis depend on the type of angiogenesis: physiological or pathological. Interestingly, the present study evaluated the current knowledge on the effects of curcumin on IUGR demonstrating acceptable potentials. Also, we tried to gather studies that had evaluated the safety of curcumin during pregnancy.

Conclusion: Gathering all the data, it seems curcumin could be an acceptable candidate for future animal and human studies on IUGR.

1. Introduction

Turmeric, as a spice and a member of the ginger family, is derived from the rhizome of *Curcuma longa* [1, 2] and has been used in traditional medicine for many centuries. According to the studies, polyphenolic non-toxic compounds of curcumin are called curcuminoids which consist of curcumin, bisdemethoxycurcumin, and demethoxy curcumin responsible for a notable range of the biological activities of curcumin [3]. Curcumin ($C_{21}H_{20}O_6$) is the main component of turmeric with numerous biological, pharmacological, and therapeutic properties [4]. So far, different studies have been conducted on the anti-inflammatory [4], anti-cancer [5], and antioxidant [6] potentials of curcumin.

Intrauterine growth restriction (IUGR) which has been defined as fetal weight less than the 10th percentile forgestational age is one of the most important issues in obstetrics and neonatology [7]. IUGR has been known as a multi-etiological condition mostly caused by genetic, placental, fetal, and maternal factors [8].

So far, various etiologies have been stated for Intra-uterine growth restriction (IUGR) with a wide variety of pathways involved in their pathogenesis. Among these pathways, impaired angiogenesis, inflammation and oxidative stress are among the most important ones. This present study would review the current knowledge regarding the possible use of curcumin as a candidate therapeutic agent for pregnancies accompanied by IUGR considering those pathways that curcumin could

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affect. Firstly, the roles of different mechanisms involving in Intra-uterine growth retardation were reviewed.

1.1. Intra-uterine growth retardation and angiogenesis

Angiogenesis, the formation of new blood (micro-) vessels from pre-existing capillaries [9] has been seen in a few physiologic situations as well as many pathologic conditions [9, 10, 11]. Growth and development of the fetus [12], female reproductive cycle [11], and wound healing [13, 14] are the most prevalent and important triggers of physiologic angiogenesis. Due to the solid role of angiogenesis in fetus growth, some literature has described IUGR as a vascular disease of the placenta [15]. There are different factors playing role in the molecular mechanism of angiogenesis with one of the most important of them being the vascular endothelial factor (VEGF). It has been demonstrated that the blood VEGF level of pregnant women has an increased pattern in up to the 30^{th}week of gestation and while facing a decreasing trend until the delivery. This pro-angiogenic factor is often regulated by a transcription factor named hypoxia-inducible factor 1-α (HIF-1α). Besides hypoxia, HIF-1α has an alternative pathway of expression dependent on ROS [16]. The expression levels of *VEGF, basic fibroblast growth factor (bFGF), and eNOS* appear to be significantly higher in the villous vascular endothelial cells, vascular smooth muscle cells, chorionic villous stromal cells, syncytiotrophoblasts, cytotrophoblasts, and extravillous trophoblasts collected from individuals with IUGR compared to those with normal pregnancy. Considering these results and the role of angiogenesis in growth and development, the authors have stated a dual role for VEGF in the pathogenesis of IUGR [15].

1.2. Intra-uterine growth retardation and inflammation

Inflammation is one of the important pathways involved in IURG pathogenesis. It has been shown that intermediate subtypes of monocytes are increased in IUGRcompared to the normal pregnant group in different weeks of pregnancy [17]. Regarding the white blood cells, myeloperoxidase (MPO), a neutrophil/monocyte-derived agent, has been noted significantly increased in pregnant women with IUGR than controls. This could indicate the role of monocytes and neutrophils in the IUGR pathogenesis [18]. An *in-vivo* study by He et al., on normal birth weight (NBW) and IUGR rats showed that the levels of interleukin 1β (IL-1β), IL-6, and tumor necrosis factor α (TNF-α) were significantly higher in the IUGR group than NBW rats [19]. Another study on the cord blood of IUGR neonates and healthy controls showed that the level of lipid peroxidation was significantly higher in IUGR cases. Also, it was shown that levels of antioxidant enzymes and antioxidant agents were significantly lower in IUGR group compared to healthy controls [20]. As has been shown, with the progression of oxidative stress or impairment of antioxidant agents, pro-inflammatory cytokines and apoptotic related pathways might get activated [21]. It seems that the oxidative stress-induced pro-inflammatory cytokines release occurs through the function of nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) [21].

Besides placental inflammation, there is evidence of systemic inflammation in neonates with IUGR. According to the studies, the levels of interferon-γ (INF-γ) were elevated in the cord serum of neonates with growth restriction compared to healthy controls [22]. Also, it has been shown that in mothers with IUGR who were stimulated by trophoblast antigens, maternal blood lymphocytes had increased levels of pro-inflammatory cytokines such as INF-γ, TNF-α, and IL-8 compared to the healthy controls. Also, other than increased pro-inflammatory cytokines, decreases of anti-inflammatory cytokines such as IL-10 were demonstrated in IUGR group [23]. Moreover, other studies have demonstrated the role of pro-inflammatory cytokines in IUGR. These factors could induce vasoconstriction in feto-placental circulation which results in placental dysfunction and therefore IUGR [23, 24, 25, 26, 27].

1.3. Intra-uterine growth retardation and oxidative stress

Oxidative stress usually caused by increased production of reactive oxygen species (ROS) and/or impairment of antioxidant agents is known to be associated with IUGR [28, 29]. Also, due to the increased activity of placental mitochondria (as well as placental-derived carbon monoxide and peroxynitrite production), pregnancy has been described as an oxidative stress condition. During the late gestational ages, excessive oxidative stress has been shown in pregnant women who presented IUGR compared to healthy controls [30]. As mentioned in the previous section, He et al., showed that the levels of IL-1β, IL-6, and TNFα were significantly higher in the IUGR group. This increase in the pro-inflammatory cytokines was observed along with increased8-hydroxy-2′-deoxyguanosine (8-OHDG or 8-oxo-dG), protein carbonyl (PC), and malondialdehyde (MDA) concentrations. Moreover, increased alanine aminotransferase (ALT) and aminotransferase (AST) activity as well as decreased liver superoxide dismutase activity were observed in the IUGR group [19]. Also, comparing the levels of urinary 8-oxo-dG in pregnant women with IUGR showed increased levels compared to normal pregnant individuals [29].

Nitric oxide (NO) is an endothelial product playing an important role in the physiology of vascular endothelium by vessels relaxation, inhibition of platelet activation and/or aggregation, decreasing pro-inflammatory gene expression, and inhibition of vascular smooth muscle cells proliferation. Any alteration in synthesis and/or inactivation of this substance could affect the mentioned events and interrupt the endothelium function [31]. In pregnancy, NO produced by uteroplacental endothelial cells plays an important role in blood supply of the fetus through controlling vasodilation [32]. According to the studies, inhibition of endothelial NOsynthase (eNOS) has been detected higher in patients with preeclampsia and IUGR compared to controls [33]. Also, another study on human umbilical vein endothelial cells found an association between decreased NO synthesis and IUGR [34]. Furthermore, alteration of platelet function has been noted as another etiology for IUGR. Enhanced or impaired platelet function may cause platelet aggregation and therefore thrombosis which has been indicated as a cause of IUGR in some cases [35, 36].

1.4. Hypothesis

Extensive studies have been performed on the effects of curcumin on a wide range of diseases, specifically inflammatory-related disorders [4]. However, so far, very few studies have focused on the possible effect of curcumin on prenatal issues. Thus, this study will review the current knowledge on the possible effects of curcumin on prevention and management of IUGR to discuss the challenges. To the best of our knowledge, this study is the first investigation on possible effects of curcumin on feto-placental outcome of IUGR with an eye on inflammation, angiogenesis, and oxidative stress.

2. Materials and methods

A narrative review study was conducted in the Maternal, Fetal, and Neonatal Research Center affiliated with Tehran University of Medical Sciences (Tehran- Iran; 2020) to investigate the possible potentials of Curcumin for pregnancies complicated by IUGR through different physiological mechanisms (Inflammation, Angiogenesis, and Oxidative Stress).

The implemented Mesh-based (Medical Subject Heading) keywords for the search were “Curcumin” OR “Turmeric” AND “Therapeutic effect” AND “Side effect” OR “Adverse effect” OR “Teratogenic effect” OR “Teratogenicity” AND “Pregnancy” AND “Intra-uterine growth restriction” OR “Intra-uterine growth retardation”, AND “Inflammation” AND “Oxidative stress” AND “Angiogenesis”. All types of human, animal, in vivo, and in vitro-based full English articles (up to 1 January 2021) including pilot study, letters to the editor, case-control, case series,

clinical trials, systematic review, and meta-analysis were selected. Cochrane Library, Scopus, IsI of Web Science, PubMed, and Google Scholar databases were used as academic search engines. Several relevant studies were also added by reviewing the reference lists. Irrelevant or duplicate investigations were excluded by reviewing the abstracts. The primary outcome was the determination of the beneficial effects of curcumin on IUGR. Also, the safety of curcumin during pregnancy was assessed as the secondary outcome.

3. Results and discussion

Reviewing included studies indicated important contributor related to possible potentials of Curcumin for pregnancies complicated by IUGR as follows;

3.1. Curcumin, angiogenesis, and IUGR

The most challenging issue regarding the use of curcumin for pregnancies suspected of IUGR is its possible effects on angiogenesis. Curcumin has been known as an angiogenesis inhibitor in different studies; however, most of the studies have evaluated pathologic angiogenesis induced by an exogenous factor [4, 37]. According to the previous sections, physiological angiogenesis could only be seen in the already mentioned few conditions. Thus, it seems that evaluating the potential of curcumin on angiogenesis should be studied on physiological angiogenesis. In a recently *in-vitro* study by Basak et al., possible angiogenic-related effects of curcumin on the HTR8/SVneo cell line (first-trimester human placental trophoblasts)were investigated (as well as HMEC-1cells: endothelial cell line). As has been shown, curcumin was able to increase and decrease the proliferation of HTR8/SVneo and the PC3 (prostate cancer) cell lines, respectively. Moreover, it was shown that tube formation of HMEC-1 cells treated withHTR8/SVneo containing media (both with and without curcumin) was significantly higher than HMEC-1 cells cultured alone. On the other hand, HMEC-1 cells treated with PC3 containing media (with a similar dose of curcumin compared to HTR8/SVneo cells) had no significant increase in tube formation compared to the HMEC-1 cells alone. Also, curcumin showed a significant increase in the healing rate of wound model ofHTR8/SVneo cells compared to untreated cells. Moreover, treating with curcumin caused an increase in VEGFA expression and VEGFR2 protein levels inHTR8/SVneo cells [38]. In the previous section, the investigation by Qi et al. was described through the oxidative stress window. They evaluated different vascular-dependent components in their experiment. It was shown that the mice model of IUGR LPD group (IUGR was induced by low protein diet) had a significantly lower blood sinusoid area while the high dose group; LPDHD group (receiving 400 mg/kg/day high dose group)experienced a significantly higher area compared to the LPD group. Also, LPLD, LPDHD, and normal protein diet (NPD)groups had no significant differences in apoptosis evaluated by TUNEL assay while the LPD group had significantly increased apoptosis compared to each of the mentioned groups. Also, *VEGF* expression analyses showed that LPHD and NPD had no significant differences while LPLD experienced higher expression of *VEGF* compared to them (LPD had a significantly lower expression level than all groups). Also, their results have shown that the expression of insulin-like growth factor 1 (IGF-1) was significantly higher in NPD compared to all groups; although, LPHD group had a significantly higher expression level compared to LPLD and LPD groups [39]. In the previous section, the effect of curcumin on the increase of *Nrf-2* expression in an *in-vivo* IUGR model was mentioned. Other than the mentioned roles in oxidative stress, Nrf-2 has been introduced as a transcriptional factor that regulates some mediators of angiogenesis [40]. As mentioned earlier; focusing on physiologically induced angiogenesis seems to be more acceptable for comparing possible effects of curcumin on angiogenesis during fetus growth. In an in-vivo study on mice ischemic wound model, You et al. demonstrated that oral treatment with curcumin could significantly increase the healing process, blood reperfusion, neovessels density of affected area compared to the controls. Also, they have shown that the ability of tube formation, migration, and proliferation of endothelial progenitor cells of the curcumin group and cells treated with curcumin in the *in-vitro* situation were significantly higher than the controls. Furthermore, curcumin was affirmed to significantly increase *VEGF* and *angiopoietin 1* (*Ang-1*) expression in comparison to the controls [41]. It was claimed that the excess platelet aggregation might affect the vascular supply through (micro-) vessels obstruction. Curcumin was shown to exert its anti-platelet activity on platelet aggregation through different agonists such as collagen, arachidonic acid, platelet-activating factor, and epinephrine [42].

It seems that curcumin acts as a double-edged sword when it comes to angiogenesis. It has been hypothesized that this diverse activity might be due to the environmental cytokines levels and/or etiology of angiogenesis. Also, the differences in the angiogenic pathways have been suggested as another possible cause. According to this theory, the pro-angiogenic activity of curcumin in wound healing is due to the direct increase of TGF-β and Ang-1 as well as activation of NF-κB which in turn induces *VEGF* and *MMP-9*expression. On the other hand, the anti-angiogenic activity of curcumin seems to be exerted through suppression of *FGF*, *MMP-2*, *COX-2* as well as *VEGF* and *MMP-9* (through inhibition of NF-κB). Unfortunately, the exact mechanism of this dual action is still unclear, however, regarding the IUGR and angiogenesis, the outcomes of the *in-vivo* studies have not shown any impaired angiogenesis [37].

3.2. Curcumin, inflammation, and IUGR

Notable numbers of studies have pointed to the anti-inflammatory properties of curcumin in the management of inflammatory-dependent chronic diseases [4, 43, 44]. Regarding the obstetric issues, an investigation has evaluated the possible effects of curcumin on monocytes released pro-inflammatory cytokines. A study was performed on monocytes from non-pregnant healthy women cultured with the plasma of normotensive pregnant individuals (control group) and women with preeclampsia. This study showed a significant increase in pro-inflammatory cytokines after treating monocytes with preeclampsia derived plasma (test group). Therein, the test group treated with different doses of curcumin showed a significant decrease in levels of IL-1β, IL-6, and TNF-α.Moreover, it was shown that curcumin can inhibit NF-κB which is the key factor for transcription of pro-inflammatory cytokines [45]. As mentioned earlier, He et al. has evaluated the role of inflammation and oxidative stress in two groups of NBW and IUGR. Also, they have used two other groups in their study: NBW (NC) and IUGR (IC) both supplemented with 400 mg/kg/day of curcumin. It was shown that the IC group had a significant lower IL-1β, IL-6, and TNF-α concentration [19]. Also, in a randomized, double-blind, clinical trial, it has been mentioned that curcumin is able to decrease MPO in comparison to the placebo group [46]. Moreover, another randomized controlled trial showed that curcumin could significantly reduce serum levels of pro-inflammatory cytokines includingTNF-α, IL-6, transforming growth factor β(TGF-β), and monocyte chemoattractant protein 1 (MCP-1)in comparison to the placebo group [47]. Furthermore, different studies have reported anti-inflammatory activity of curcumin through suppression of IL-2, IL-5, IL-8, IL-12, IL-18, and monocyte inflammatory protein-1 alpha (MIP-1α) [48]. Moreover, this compound could inhibit lipoxygenase (LOX), phospholipases A2 (PLA2), and cyclooxygenase-2 (COX-2) activity which are important role players of inflammation. Curcumin can also induce NOS activity to increase levels of suppressed NO [48, 49]. It has been, as well, successfully used in many trials for inflammatory-dependent diseases such as inflammatory bowel disease (IBD), arthritis, uveitis, post-operative inflammation, idiopathic orbital inflammatory pseudotumor, and psoriasis as well as many other ones

[50]. Thus, it seems that curcumin might be a potential therapeutic agent for the treatment of IUGR due to its anti-inflammatory properties.

3.3. Curcumin, oxidative stress, and IUGR

So far, different *in-vitro* and *in-vivo* studies have shown the antioxidant effects of curcuminin different pathological conditions through different pathways [51]. In the study by He et al. a significant decrease inpro-inflammatory cytokines concentrations in IUGR animals has been shown. The authors also detected significantly decreased levels of AST (serum), ALT (serum), 8-OHDG (liver), PC (liver), and MDA (liver). Moreover, the hepatic glutathione redox cycle was significantly improved in the IC group compared to the IUGR group. Through further evaluations, they cleared the role of NF-κB, nuclear factor erythroid 2-related factor 2-like 2/antioxidant response element (Nrf2l2/ARE), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways in the mentioned antioxidant and anti-inflammatory changes [19]. A similar significant decrease was found in an in-vivo model for IUGR. Niu et al., demonstrated that curcumin supplement could significantly reduce the levels of lipid peroxidation metabolites including MDA and H_2O_2. Also, the after-birth evaluations showed an increased feed intake and body weight in IUGR cases treated with curcumin caused by improved activation of serum and liver antioxidant enzymes as well as up-regulation of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 [52]. Another study by Qi et al. on a mice model of IUGR (induced by low protein diet; LPD) compared outcomes of treatment with 100 mg/kg/day (low dose group: LPLD) and 400 mg/kg/day (high dose group: LPDHD) of curcumin with the LPD and normal protein diet (NPD) groups. It was shown that the LPLD and LPHD groups both had significantly higher birth weights than the LPD group. Also, the LPDHD group exhibited no significant difference in birth weight compared to the NPD group. Also, serum cortisone levels were significantly lower in the LPDHD and LPLD groups compared to the LPDs (no significant differences were observed with the NPD group). Moreover, they clearly demonstrated the antioxidant activity and ROS scavenger potential of curcumin induced by *Nrf2, catalase* (*CTA*), and *heme oxygenase-1* (*HO-1*) expression, as well as a decrease in MDA content [53]. Also, an *in*-vivo study has shown that curcumin is able to decrease 8-oxodGaccumulation as well as inducing the expression of oxidant-generating genes (such as *COX-2*), malondialdehyde, and plasma nitrate [54]. Moreover, curcumin has been successfully used in different trials as an antioxidant agent for diseases such as non-alcoholic fatty liver disease [55], metabolic syndrome [56], tropical pancreatitis [57], and many other diseases [50].

3.4. Curcumin and pregnancy

Using therapeutic effects of Curcumin during pregnancy needs several considerations. So far, Curcumin has been investigated in many trials for many diseases/disorders in various doses and different forms such as extract, liposomal enclosed, and nanoparticles attached [50]. *A meta*--analysis has been performed on 7trials (total number of 649 cases) regarding the possible effects of curcumin on impaired lipid profile of patients with metabolic syndrome and type 2 diabetes mellitus. The mentioned study showed that no serious side effects observed in any of the studies and minor side effects only were found in five of eight trials which one of them failed to express the exact number of side effects. In four trials, only8 cases of dyspepsia, nausea, constipation, hot flash, and abdominal pain were reported as the side effect [58]. Unfortunately, no clinical evaluation has been performed on curcumin safe and/or toxic doses in pregnancy or its possible effects on the fetus to this date. However, several *in-vivo* studies have claimed no significant teratogenic/adverse effects associated with curcumin consumption on pregnancy outcomes. It was shown that oral administration of 0.5% of turmeric equal to 0.015% curcumin for 12 weeks made no significant change in the implantation rate, number of dead and live, chromosomal abnormality, and bodyweight of both rats and mice embryos [59]. As it has been reported by Ginger et al., low (1500 ppm), medium (3000 ppm), and high (10,000 ppm almost equal to 1000 mg/kg/day)doses of curcumin fed to both male and female rats did not reveal any reproductive toxic effect on the offspring in their two next generations [59, 60]. Another *in-vivo* study on pregnant rats by Kumar et al. demonstrated no teratogenic effects such as stunted growth, curling of the tail, lip, wrist drop and exencephaly, cleft palate, and abnormal bone ossification on the offspring treated with different doses of curcumin (100, 150, and 200 mg/kg/day). Moreover, they have shown that curcumin could significantly decrease mentioned fetal anomalies as well as a causing a significant increase in live births, body weight, crown to rump length in valproic acid-treated pregnant animals. The mentioned protective effects are believed to be achieved through decreasing *CYP2C9* expression, ROS, and thiobarbituric acid reactive substances (TBARS) as well as a significant increase in superoxide dismutase (SOD), reduced glutathione (GSH), and CAT [61].

3.5. Pharmacokinetics barriers and solutions

Furthermore, pharmacokinetic and pharmacodynamics properties of curcumin may be influenced by gestational changes. It was reported that up to 12 g/day could be well tolerated without any adverse effects; however, the absorption of this compound is too negligible. Excretion of high percentages of ingested curcumin in the feces and biliary ducts, instability in different biological environments and degradation were responsible for its poor absorption and bioavailability. With respect to metabolism of curcumin, the majority of this molecule was rapidly metabolized in the liver by liver microsomes, alcohol dehydrogenase, glucuronides, and sulfates. Regarding the bioactivity of metabolites of curcumin and their effects, on the other hand, there are not well-documented findings. Hence, no appreciable and predictable levels of curcumin compound could be detected in the heart blood or tissue organs. Eliminating this limitation related to low bioavailability, combining curcumin with other chemical substances like piperine has been suggested. Piperine inhibits hepatic and intestinal degradation of curcumin leading to increase of its serum levels and bioavailability [62, 63]. Also, to overcome this limitation, there has been different studies performed on curcumin to increase its bioviability which one of them is nanoparticle addition. So far, different nanoparticles such as gold, glyceryl monoleate, chitosan, silica, poly (2-hydroxyethyl methacrylate), casein, and cyclodextran have used. Also, curcumin has been encapsulated with poly lactic-co-glycolic acid, polymers, and oil bodies. Furthermore, so many other forms of this molecule have been used in both clinic and market which significantly have increased its bioviability [64]. Variations of each stage of pharmacokinetic parameters during pregnancy can also significantly alter the bioavailability of curcumin. Nausea/vomiting in early pregnancy, decrease of gastric acid and intestinal motility, increase of plasma volume, cardiac output and intestinal blood flow, decrease of plasma protein binding, alteration in drug metabolism and clearance (by liver, intestine and the placenta), secretion, and reabsorption are some factors that may influence the drug bioavailability [3].

4. Conclusion

Herein, three of the main pathways involved in IUGR were discussed: impaired angiogenesis, inflammation, and oxidative stress. Apparently, some of the molecular mechanisms involved in each of the pathways are related to other ones. Thus, it seems that IUGR might be caused by a single etiology (or not), but it is accompanied by different pathways which would therefore require multi-target therapy. According to the reviewed literature, curcumin suppresses inflammation and oxidative stress; however, data on angiogenesis is not as solid as other pathways. On the other hand, different *in*-vivo reports are addressing not only the safety of some doses of curcumin but also its potential in improving IUGR

in the same doses. Although these data are not enough for making a clinical decision, it seems that future and complementary *in-vivo* and following it clinical studies (for safety and dosing during pregnancy) might be helpful for a better insight regarding the future of curcumin as a possible treatment for IUGR.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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