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Future Therapeutic Strategies in the Glaucoma Management

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Glaucoma is a group of eye diseases in which progressive damage to the ocular nerves may cause retinal ganglion cell (RGC) death. Worldwide glaucoma is a leading cause of avoidable blindness. Intraocular pressure (IOP) is considering to be the main identified cause of danger so far, and lowering intraocular pressure is the only recognized technique for inhibiting disease progression. Furthermore, blood vessels and genetic components of glaucoma are considered additional risk factors. In order to realize the potential progress of glaucoma treatment, new treatment strategies and ambitious goals are constantly being developing. These treatments will provide specific tissue goals to reduce IOP and ensure neuroprotective effects on RGCs. Consequently, physicians can shortly have an expanded range of medical choices to choose from, coupled with therapies that are more successful. Therefore, this study has reviewed the recent studies that were conducted on cellular mechanisms of glaucoma treatment.

Keywords: Glaucoma; RGCs; intraocular pressure; treatment.

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1. INTRODUCTION

Glaucoma refers to a series of eye diseases that can cause progressive damage to the optic nerve and may cause RGC death. According to a 2010 report by the World Health Organization, glaucoma accounts for 2% of visual disability and 8% of total blindness. Due to the growth of population, the total number of glaucoma patients is expecting to be increased [1,2]. The classification of glaucoma depends on the condition of the drainage route. The drainage pathway of open-angle glaucoma looks normal, while the drainage pathway of closed-angle glaucoma is blocked. Glaucoma was moreover categorized to the primary and secondary glaucoma. The most common subtype of glaucoma is primary open-angle glaucoma. Therefore, glaucoma is associated with increased intraocular pressure, and current drugs that lower intraocular pressure are still the only clinically proven treatment for glaucoma [3]. The focus of the current review is to briefly summarize and discuss the new goals for reducing IOP.

2. CURRENT TREATMENT STRATEGIES FOR GLAUCOMA

Glaucoma is a disease that is not well understood, but the main goal of treatment is to reduce intraocular pressure [3,4]. A 40% reduction in intraocular pressure will reduce the progress of the ocular loss by about half. The first drug for glaucoma was released in 1875, and now there are many IOP eye drops for reducing glaucoma. Compromise options for ophthalmic classification: beta blockers, prostaglandin analogues, carbonic anhydrase inhibitors, and α2-sympathomimetic receptor agonists [5], as shown in Table 1.

3. FUTURE THERAPY PLANS FOR GLAUCOMA

The pathogenesis of glaucoma includes many mechanisms. However, no one seems to fully

Table 1. Anti-glaucomatous agents and their influences on aqueous humour pathway [7]

Compound	IOP (%)	Aqueous production (%)	Aqueous out-flow (%)
β-blocker (non-selective)	↓ 25	↓33	
β-blocker (β1-selective)	↓ 20	↓ 24	
Direct miotic agents	↓ 20		↓ 24
adrenergic agonist (non-selective)	↓ 20		↓
α2-agonist (selective)	↓25	↓ 35	
Inhibitors of Carbonic anhydrase	↓ 25	↓ 35	
Analogues of prostaglandin	↓ 30		↓ 100

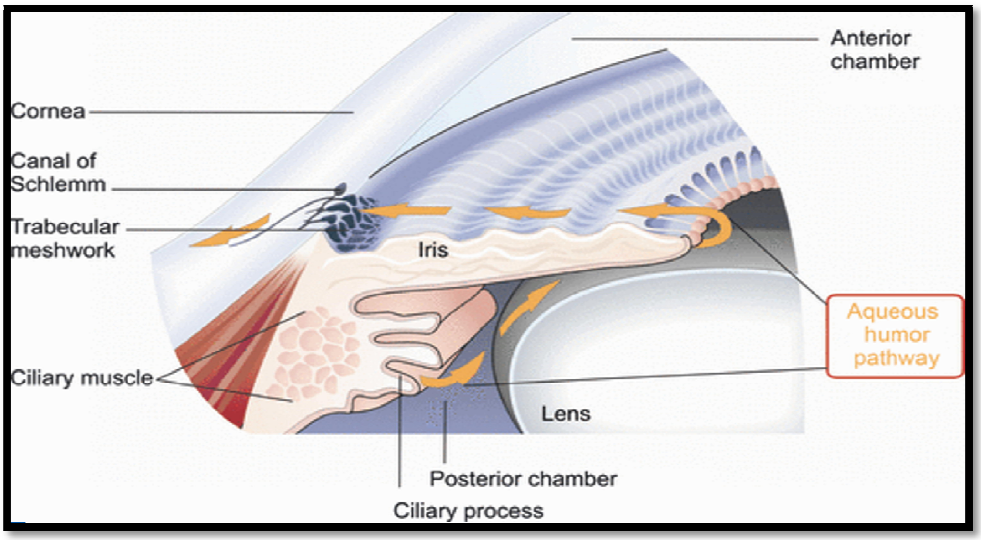

Fig. 1. Anatomy of the human aqueous humour pathway [8]

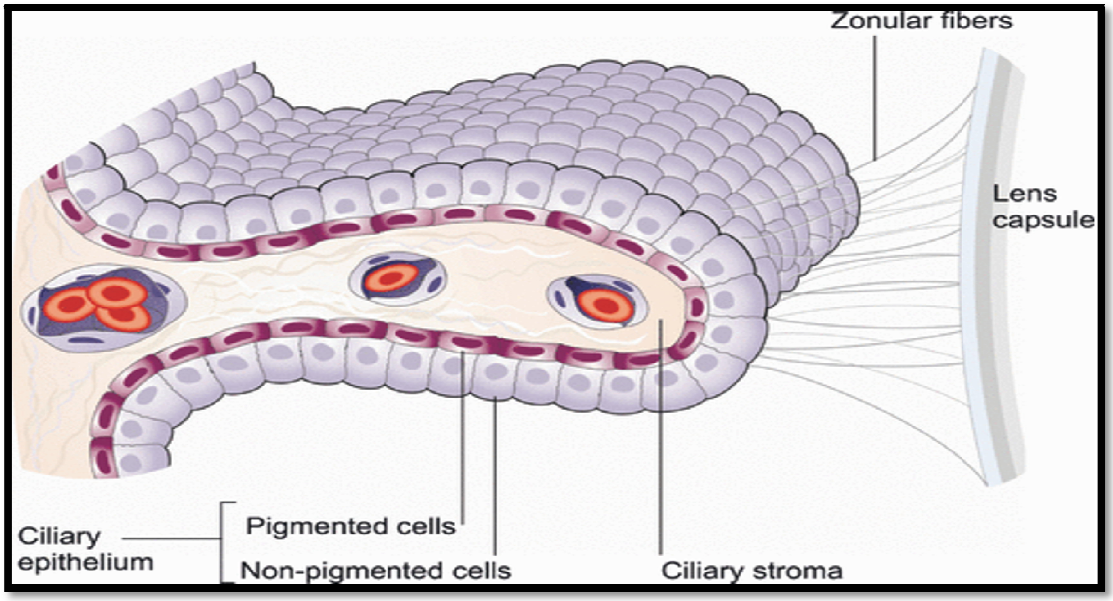

Fig. 2. Anatomy of a ciliary process [8]

describe the disease, and different etiologies have carried out key trials in the progress of new anti-glaucoma strategies. In this part, treatment plans can emphasize on IOP lowering approach, therefore, an effort has been done to discover novel, curative goal to lower synthesis of aqueous humor (AqH) (Figs. 1 and 2) or to promote the uveoscleral outflow into the anterior chamber angle using assorted subcellular pathways from those already existing [6].

4. NITRIC OXIDE

The endogenous signaling molecule is called nitric oxide (NO), which is a new goal to reduce IOP [9]. In many tissues of the eye, both the anterior and posterior endogenously produce NO, and it has a stimulator of the intracellular receptor soluble guanylate cyclase (GC). The latest evidence links NO to GC through the IOP director and the enzyme cyclic guanosine monophosphate (cGMP) pathway in glaucoma's retinal pathophysiology. There are cumulative signs that the direct guide to intraocular pressure is NO, and the failure of the NO-sensitive soluble GC-1 (NO-GC1) pathway is associated with glaucoma. Ciliary body (CB), the trabecular meshwork (TM), and the Schlemm's canal (SC) are tissues able to generate NO in normal eyes [10]. In some cases, the impact of NO on IOP is related to the activities of the downstream second messenger cGMP, mainly in the usual outflow route. Taking of NO-generating compounds to encourage the NO-GC1- cGMP pathway can reduce IOP through TM relaxation, TM volume changes, and increased SC cell permeability [11–14]. "Many studies conducted in rabbits have shown that NO donors and cGMP analogues can significantly reduce IOP and lead to increase outflow facilities [15]. In a dose-dependent manner, the intravitreal or intraluminal injection of a cGMP analog named 8-Br-cGMP may increase the AqH outflow facility [16]. The 8-Br-cGMP is an activator of cGMP enzyme, it can easily penetrate cells, and its hydrolysis by phosphodiesterases is less sensitive than that of native cGMP [17]. When used in low doses, 8-Br-cGMP will show a decrease in AqH flow, but the outflow facility will not be affected. On the other hand, 8-Br-cGMP displays an improvement in outflow facility at high doses. One possible mechanism for promoting the inhibitory effect of NO on AqH synthesis includes the inhibition of Na, K-ATPase (NKA) pumps. In the ocular tissues, NKA is the main active transporter involved in the formation of ion gradients that control the formation of AqH [18]. Ouabain lowers the secretion of AqH by about 62% by inhibiting the NKA pump. In addition, the use of sodium nitroprusside (SNP) on bovine and porcine eyes cut the second messenger cGMP and protein kinase G, thereby inhibiting NKA pump thereby inhibiting the secretion of AqH, and thus reducing IOP[19].

5. PHOSPHODIESTERASES-5 INHIBITOR

A family of enzymes that control intracellular levels of the second messenger's cyclic adenosine monophosphate (cAMP) and cGMP is called phosphodiesterases. The first phosphor-diesterase inhibitor was recognized in 1970 and up to the present time, 12 dissimilar isoenzymes were recognized [20]. Phospho-diesterase (PDE) is found in every cell in the body. However, the distribution of isoenzymes differs between the tissues. There are 11 types of PDE, some of which highly selective for cGMP such as PDE5, 6 and 9, other types have coupled specificity for both cGMP and cAMP such as PDE1, 2 and 11 and others have selective cAMP but sensitive cGMP such as PDE3 and 10. The production of cGMP induces PDE5 activity by allosteric integration of cGMP into the GAF regulatory tandem domain. The enzyme catalytic rate and affinity are increased due to cGMP attachment to the PDE5 GAF domain. At the same time, cGMP-dependent protein kinase (cGK I) phosphorylates PDE5 in its N-terminal region. After phosphorylation, the most likely cause of prolonged PDE5 activation is increased sympathy of cGMP. The regulation of the signaling sensitivity of NO/cGMP in platelets is controlled by a feedback mechanism, and manifests as a temporary form of cGMP response (rapid increase in cGMP and hydrolysis) [20]. Furthermore, this mechanism is also explaining the desensitization induction by NO - the decreased cGMP quantity next to second stimulation by NO- [21]. The efficiency of PDE5 inhibitors depends on the manufacturing capacity of cGMP, and the fact that PDE5 closely interacts with NO/cGMP signaling is well accepted. The effectiveness of PDE5 inhibitors depends on the ability of cGMP to construct. This is because PDE5 enzymes are closely related to NO/cGMP signaling. Nitric oxide synthase (NOS) inhibition retract the synthesis of NO and subsequent cGMP production, thus inhibiting of the vascular dilation effect through PDE5 inhibition. Inhibition of PDE expected to be less applicable in locations related with diminished NOS action, such as endothelial function impairment. On the other hand, sildenafil-PDE5 inhibitors-can effectively enhance the effects of NO-producing compounds [21]. Therefore, patients taking organic nitrates and sildenafil have severely reduced blood pressure. In Rabbits, inhibition of PDE-5 produce important IOP reduction, such effect endorsed by topical administration of sildenafil ophthalmic solution (0.3%) in both normotensive and corticosteroid induced hypertensive rabbit's eyes [22], this study suggests that sildenafil could be considered as an inhibitory modulator of AH production by decreasing intracellular Ca^{+2} [23]. In addition to the above, sildenafil can also increase AH outflow and uveoscleral outflow [24]. Other suggested mechanism by which sildenafil can inhibit AH secretion by blocking NKA pump in NPE as a result of cGMP elevation [25]. This mechanism is consistent with Ellis and colleagues who reported that elevated cGMP inhibits NKA in the choroid plexus and CB [26]. Therefore, this study suggests that increasing cGMP as a result of using sildenafil may reduce IOP.

6. NA, K-ATPASE ENZYME

About 60 years ago, Skou discovered NKA pump, which can be used as a molecular tool to transport Na + and K + through cell membranes. NKA is a part of the P-type ATPase family. NKA is a protein complex molecule widely distributed in cell membranes, with two non-covalently linked subunits α and β [27]. Subunit α which contains adenosine triphosphate (ATP) and other ligand attachment sites is designed as a catalytic subunit. The role of β subunit is vital for the membrane focusing and full participation of the NKA. Four protein isoforms of NKA have been recognized. In 1987, Michael Marks and Nicholas Seeds were found to have various isoforms. Digoxin and ouabain (plant-derived cardiac steroids) are known to be inhibitors of NKA pumps. Over 200 years, digoxin has used widely for congestive heart failure management. However, it was not until the detection of NKA pumps in the 1950s that the exact mechanism by which digitalis soared to inhibit NKA was documented [28]. The pigmented cells of the ciliary epithelium express $\alpha 1\beta 1$ isoform of, whereas the nonpigmented cells of the ciliary epithelium show $\alpha 2\beta 3$ isoform of NKA. With limited rare local and systemic toxicity, the selective inhibition of $\alpha 2$ isoform can effectively go lower. Earlier trials using recombinant human isoforms of $\alpha 1\beta 1$, $\alpha 2\beta 1$, and $\alpha 3\beta 1$displayed digoxin with selective $\alpha 2$ activity due to its trisdigitoxose moiety [29]. This fact led to a likelihood that alteration of the trisdigitoxose might elevate the selectivity towered α 2. Several derivatives display greater selectivity for $\alpha 2$ over $\alpha 1$, nearly 8-fold. In rabbits, the effect of topical administration of cardiac glycosides on IOP has been considered by inhibiting or reversing the ability to use A3 adenosine receptor selective

agonists to induce a critical increase in IOP [30]. Digoxin derivatives with relatively α2-selective activity shows more IOP lowering effect when compared to that of digoxin, digoxigenin, or ouabain. Therefore, due to the main role of α2 in the production of AqH, α2-selective derivatives of digoxin may become a new therapy for regulating IOP [29]. Furthermore, a study done by Waleed et al. endorsed that topical application of digoxin (0.00625%) ophthalmic solution reduces IOP significantly in both normotensive and betamethasone induced hypertensive rabbits eyes [31]. Other studies have shown that the administration of low and non-toxic concentrations of ouabain increases AqH outflow. The researchers studied other mechanisms of action of ouabain's effectiveness. Simon and colleagues demonstrated the ability of ouabain to reduce IOP by attaching and preventing the NKA pump in the ciliary process of the eye [32]. NKA enhances the transfer of two K^+ from the outside space into the cell and the removal of three Na^+ from the cell, while hydrolyzing ATP to ADP and inorganic phosphate (Pi). The emergence of electrochemical gradients represents the main energy source used by transportation equipment to drive ions through AqH to form the required transepithelial transportation [33]. In addition, research shows that the combination of ouabain and NKA may control cytoskeletal proteins, thereby changing the morphology of cells [34].

7. CALCIUM CHANNEL BLOCKER

Calcium is a vital intracellular messenger [35] and influx of Ca^{2+} could have many effects on the dynamics of AqH, comprising ciliary perfusion as well as hydrostatic and osmotic component. Calcium channel blockers (CCBs) are drugs often used to treat hypertension and coronary artery disease [36] and to reduce vascular tone by reducing Ca^{2+} influx leads to vasodilation and raising in the local blood flow in many tissues constituting the head of ocular nerve. It can also show another beneficial effect of CCB by inhibiting the synthesis of extracellular matrix collagen [37]. Trabecular meshwork cell relaxation increases the outflow facility of AqH by blocking the L-type channel also produced by CCB. Perfusion experiment work with verapamil administration in the incised human eye showed a dose-related increase in the outflow facility. Most studies conducted in laboratory animals and humans believe that local CCB (eg, nimodipine, verapamil, diltiazem, nifedipine, or flunarizine) reduces IOP. Topical diltiazem can minimize intraocular pressure (approximately 5 mmHg) in normal rabbits [38]; (4 mmHg)in the betamethasone-induced ocular hypertensive rabbits [39]. Topical application of diltiazem can respectively reduce the intraocular pressure of normal, betamethasone induced intraocular hypertension and water load induced intraocular pressure (6 mmHg; 4 mmHg and 5 mmHg) [40], while normal cynomolgus monkey's IOP decreased the most (4 mmHg, [41]. Maximum intraocular pressure reduction after local application of nifedipine is (6 mmHg) in normal rabbits [38] and (5 mmHg) in cynomolgus monkeys. Netland and colleagues showed that verapamil infusion can reduce intraocular pressure in normal people and cynomolgus monkeys, and has a beneficial effect on the posterior bulb or optic nerve head circulation [42]. Other studies have shown that verapamil can reduce IOP in normal people by about 3 mmHg [43]; normal cynomolgus monkeys are 2.6 mmHg [41]; and 6 mmHg in normal rabbits [38]. In 12 patients with intraocular hypertension, a single local application of verapamil 0.125% can encourage a reduction in IOP of 3 to 4 mm Hg for 10 hours, while a simple drop was detected in normal IOP volunteers (≈1.5mm Hg) [44]. In patients with high intraocular pressure, topical application of 0.125% verapamil for 14 days can reduce IOP by about 7.0 ± 2.9 mm Hg [45]. Sunil and his colleagues showed that topical application of diltiazem (0.5%) and diltiazem (0.125%) in corticosteroid-induced glaucoma for 12 days can reduce intraocular pressure by about 8.0 and 9.6 mmHg, respectively [46]. Researcher Waleed and colleagues showed in a study that after one day of topical eye drops (0.5%) of nimodipine can reduce IOP by (9.09%) in normotensive and (19.29%) in betamethasone -induced hypertensive rabbits eyes. Also, the peak IOP decline achieved after 4 days of installation in both normotensive (16.16%) and hypertensive (22.86%) models [47]. Flunarizine with sodium channel blocking activity, L-type and T-type calcium channel blockers have good ocular bioavailability, and the maximum IOP reduction when applied topically is 2-5 mmHg ;10 mmHg; 4 mmHg [41] and 5 mmHg in normal rabbits, chymotrypsin- induced ocular hypertensive rabbits [48]; normal cynomolgus monkeys and unilateral laser-induced ocular hypertensive cynomolgus monkeys [49] respectively. Additionally, due to its inhibition of calcium and sodium influx, flunarizine shows a protective effect on retinal injury that induced by intravitreal injection of N-methyl-D- aspartic acid (NMDA) [50]. Similarly, for patients with normal

tension glaucoma (NTG), oral flunarizine also shows important significance for retrobulbar hemodynamics. In addition, flunarizine inhibits the contraction of human trabecular meshwork cells induced by ET-1. CCB interferes with gap junctions or cation transport in ciliary epithelial cells, resulting in reduced AqH synthesis [51].

8. RENIN-ANGIOTENSIN SYSTEM

The circulating renin-angiotensin system (RAS) plays an important role in regulating blood pressure and fluid balance. The peptide angiotensin II (Ang II), the angiotensin-converting enzyme (ACE1) and the angiotensin receptor type1 (AT1) are chiefly guiding by RAS. Vasoconstriction, stimulation of the sympathetic nervous system and stimulation of aldosterone production are the main effects of Ang II though which it controls the blood pressure [52]. Tissue AT1 receptor is the main targets of Ang II. As stated in the new confirmation, it is believed that the increase in blood pressure in the elderly is not only regulated by circulating RAS, but that autocrine or paracrine of local RAS also plays a vital role in controlling blood pressure.. Therefore, not only Ang II and ACE1 found in tissues are involved in controlling blood pressure, but also angiotensin (1-7) [53]. As a result from mentioned studies, the treatment of hypertensive patient must focusing on desired actions that resulted from stimulation of Ang(1–7)- ACE2 Mas axis, as well as suppression of the normal AT1- Ang II- ACE1 axis. Recently, RAS in the eye tissue of non-pigmented and colored epithelial cells plays an important role in the formation and drainage of AqH. Ang II opens potassium channels and stimulates aldosterone production by triggering the Ca^{2+} signaling system. The volume of cell loss that accompanies the mentioned effects indicates that Ang II has secretagogue activity in NPEC [54]. Additionally, the activation of Na^{+}/H^{+} exchange by Ang II will lead to an increase in Na^{+} cytoplasmic concentration. There is a link between the sodium and the pathological factors in epithelia of both renal tubules and CB, which give a reason of the concurrence of systemic hypertension and glaucoma [54]. Furthermore, RAS plays an essential role in the outflow of AqH from TM. Inducing cell proliferation in bovine and in vitro by stimulating collagen synthesis is the recommended role of Ang II [55]. Furthermore, intracamerally administration of Ang II able to reduce the uveoscleral outflow [56]. The application of both natural and synthetic Ang II to human eyes and cat eyes can reduce IOP, with the same reduction effect observed in *in vivo* and in vitro studies. Iris artery vasoconstriction is the mechanism by which it reduces the IOP [56]. Human studies have shown that although the effect of lowering blood pressure is only shown in patients with arterial hypertension, ACE1 inhibitors or angiotensin type- 2 receptor blockers can reduce intraocular pressure in glaucoma and normal tension glaucoma patients In both glaucoma models (acute and chronic), perindopril has an ocular hypotensive effect on rabbits [57]. ACE1 inhibitors can diminishing the AqH formation in the CB by reducing blood flow. ACE1 inhibitors promote the formation of prostaglandins by inhibiting the breakdown of bradykinin, which may result in decreased intraocular pressure by promoting the outflow of the uveal scleral area. The inhibiting effects on bradykinin breakdown by ACE inhibitors also stimulate prostanoids vasodilation effects and the NO pathway, as well as decrease the synthesis of the endothelin-1, a vasoconstrictive peptide that shown to display contraction activity in both porcine and in the human ophthalmic ciliary epithelium. Specifically, for glaucoma losartan has ability to decrease normal or elevated IOP in humans IOP [58]. Similarly, in animal models that induce an increase in IOP, olmesartan can reduce IOP. In addition to reducing the effect of IOP, the neuroprotective activity shown during the use of ARB in the glaucoma environment. Candesartan has been displayed to reduce RGC loss in rats with increased intraocular pressure and normal glaucoma. Furthermore, losartan when given to the mouse eyes with raised IOP shows a neuroprotective activity on RGCs [59]. A study showed that after one day of infusion of telmisartan eye drops (1%), significantly reduced IOP(12%) in betamethasone- hypertensive rabbit eyes and reached a maximum IOP reduction (20.33%) after 7 days of infusion [60]. Captopril administration continuously to the rat with chronic model of glaucoma showed an important neuroprotection activity against RGC loss [61]. In addition to its role in balancing intraocular fluids, local RAS also plays a key role in the development of diabetic retinopathy. Recently, a prorenin receptor found in Mueller's retinal cells is involved in the development of neovascular pathology, and the inhibitory effect of these receptors has shown beneficial effects on diabetic retinopathy [62]. From the mentioned findings, we conclude the role of RAS in reducing IOP. New options for glaucoma treatment focus on increasing the activity of ACE2, Ang (1-7) and Mas receptors. What's more, RAS acting

compounds exert a beneficial role in neuroprotection activities.

9. CONCLUSION

This review focuses on novel treatment strategies and possible expected mechanisms to reduce IOP. Many new targets for glaucoma treatment submitted, but up to now the merely available compounds for glaucoma treatment focusing on lowering IOP, which are diminishing the disease progression rate. Taking everything into consideration, in the foreseeable future, ophthalmologists is expected to have an enlarged number of glaucoma treatment options and even curative. Beyond doubt, too much attention must be paid to any replacement of classic treatments by new therapies.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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