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ORIGINAL ARTICLE

Evaluation of the effectiveness of epigallocatechin gallic acid, resveratrol, and autologous serum in an alkaline eye injury model

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Abstract

Purpose: To compare the efficacy of green tea extract (epigallocatechin gallate – EGCG) and resveratrol with autologous serum (AS) in a chemical eye injury.

Methods: A total of 17 New Zealand rabbits were divided into 5 groups (3 treatment groups, 1 sham, and 1 control group). A membrane filter paper impregnated with 10% potassium hydroxide was placed over the right eyes of the rabbits under sedation for 30 seconds to induce a chemical burn. Next, the ocular surfaces were washed with 0.9% saline for 10 minutes. EGCG solution was applied to the rabbits in Group 1, resveratrol solution to Group 2, and 20% AS to Group 3 for 3 weeks. In all groups, 0.9% saline was applied to the left eyes for 3 weeks (sham). Two corneas were left untreated after the chemical burn as a control. All groups were photographed daily for 3 weeks. Afterwards, the rabbits were sacrificed, the corneas were excised, and examined histopathologically with Hematoxylin & Eosin, Masson Trichrome, PAS staining, and immunohistochemically for GFAP, Ki-67, NF-kB, and IL-17 expression.

Results: Clinically: AS was the only agent that clinically decreased the epithelial defect compared to the pre-treatment status.

Histologically: Neuronal regeneration was higher in Group 2. Innate immune and inflammatory responses, as well as regeneration, were superior in Group 1.

Conclusion: EGCG and AS, but not resveratrol, could stimulate corneal healing in chemical eye injuries. More studies are needed to determine the optimal dose of EGCG and obtain a clinical response.

Keywords: Epigallocatechin gallic acid; ocular burn; ocular chemical injury; resveratrol.

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Chemical corneal injuries are ophthalmological emergencies that require rapid treatment and close monitoring. They constitute 11–22% of all ocular traumas and tend to be more prevalent in low socioeconomic populations and in men.[1-3] The most common agents that cause chemical injuries are alkaline compounds, followed by acidic compounds and alcohol. Although both alkaline and acidic compounds affect the ocular surface, the damage resulting from exposure to alkaline compounds is usually more severe.[1-3]

Treatment for corneal injuries relies on the stimulation of epithelialization of the ocular surface, decrease in inflammation, and prevention of complications as much as possible.[1,2] However, the agents that are currently available do not provide an adequate level of treatment. For this reason, a significant number of patients have to continue their lives with visual acuity at legal blindness levels despite undergoing treatments. Therefore, new therapeutic agents and applications are still needed.

Epigallocatechin gallate (EGCG) is a polyphenolic natural compound and belongs to the catechin family. EGCG has been shown to decrease proliferation in both diseased and normal cells and may protect from both genetic mutations and inflammation.[4-6] It is used as an additive in chemical preservatives due to its antioxidant properties. EGCG was reported to be beneficial for dry eye and corneal epithelium damage.[7-9]

Resveratrol is a natural polyphenolic compound that is found in foods such as black grapes, blueberries, black mulberries, sweet potatoes, and peanuts. One of the mechanisms by which it prevents cell proliferation is by inhibiting the histone deacetylase enzyme. Resveratrol has anti-inflammatory, antioxidant, anti-angiogenic, and neuroprotective effects.[10,11] Resveratrol can also increase epithelialization by stimulating the expression of NOTCH, which is known to affect epithelial maturation.[12] Due to these properties, resveratrol has been used as a treatment option in uveitis, diabetic retinopathy, dry eye, and corneal trauma.[13-15]

The present study aimed to evaluate the efficacy of EGCG and resveratrol in a model of chemical corneal trauma; autologous serum (AS) was used as the reference treatment for comparison.

Materials and Methods

A total of 17 New Zealand rabbits were divided into 5 groups. The right ocular surfaces were exposed to 10% potassium hydroxide to induce burn in rabbits assigned to Groups 1, 2, and 3 (n=5 for each group). Group 4 included the left eyes of these rabbits, which were not exposed to chemicals and were solely treated with saline. The control group included the right eyes of two rabbits that were exposed to chemical burn and treated with saline alone. Each solution was administered in 50 µl doses three times a day.

All rabbits were sedated with 35–50 mg/kg ketamine and 5–10 mg/kg xylazine applied subcutaneously. Next, filter papers impregnated with 10% potassium hydroxide were applied to the right eyes of the rabbits in all 5 groups for 30 seconds to model a chemical burn. Following this, the ocular surface was washed with 0.9% physiological saline for 10 minutes. The chemically injured right eyes in Group 1 animals received EGCG, Group 2 received resveratrol, and Group 3 received AS solutions for 3 weeks. The uninjured left eyes of these rabbits were taken as a sham group and received 0.9% physiological saline for 3 weeks. The animals in the control group received 0.9% physiological saline to the right eyes 4 times a day for 3 weeks.

The clinical appearance of the corneas was documented by photography on the 1st, 7th, 14th, and 21st days in all groups (12 MP, f/1.6, 26 mm sides, 1/2.55", 1.4 µm, dual pixel with LIDAR scanner) with 5× magnification. Inflammation was determined by considering the following parameters:

1. Conjunctival hyperemia (normal = absent; mild = mild or sectoral engorgement of the conjunctival vessels; moderate = diffuse engorgement of the conjunctival vessels; severe = significant engorgement of conjunctival vessels).
2. Corneal edema (normal = absent; mild = present with visible iris details; moderate = present without iris details; severe = present without visible pupil).
3. Corneal epithelial defect (normal = absent; mild = defect involving less than one quarter of the corneal surface; moderate = defect involving one quarter to one half of the corneal surface; severe = defect involving more than one half of the corneal surface).[14]

At the end of the experiment, all rabbits were sacrificed, and the corneas were excised for histological examination. The staging was applied by two ophthalmologists who were blinded to the study groups.

Resveratrol and EGCG extracts were obtained from Sigma-Aldrich® (Massachusetts, USA). The extracts were individually added to 0.9% NaCl (physiological serum) solution at a concentration of 5 µM and 10 mg/ml, respectively, and filter sterilized. The solutions were prepared with the support of the Pharmacognosy

Department. The blood samples obtained from rabbits were centrifuged at the Department of Ophthalmology and diluted with sterile saline solution at a ratio of 1:5 to obtain the AS solution.

Histopathological and immunopathological evaluation of the corneal samples was carried out at the Department of Histology and Embryology. Histopathological examinations were carried out with Hematoxylin & Eosin, Masson Trichrome, and PAS staining. Immunohistochemical examinations were carried out with the markers GFAP, Ki-67, NF-kB, and IL-17. The presence of every brown cytoplasmic staining cell was scored as positive. The number of GFAP, IL-17, NF-kB, or Ki-67 immune-stained stromal and epithelial cells was assessed systematically by scoring at least 100 cells per 10 fields of tissue sections at 100× magnification by two histologists who were blinded to the study groups.

The current study was conducted with the approval of the Ege University Animal Experiments Ethics Committee. The study adhered to the ARVO Animal Statement.

Statistical Analysis

The data were evaluated with SPSS 22® (IBM, New York, USA) software. Since the data did not show normal distribution, the Kruskal–Wallis test in independent multiple groups and the Friedman test in dependent multiple groups were used. Wilcoxon and Mann–Whitney U tests were used for between-group comparisons, depending on whether they were dependent or independent, respectively.

Results

1) Clinical Evaluation

After chemical damage was created, statistical evaluation was made between the groups in terms of conjunctival hyperemia, corneal edema, and corneal epithelial defect. Although there were clinical differences between the groups in corneal edema resulting from chemical damage, the pre- and post-treatment conditions of each group were statistically evaluated within themselves; therefore, their effects on corneal edema were examined more precisely.

No significant difference in conjunctival hyperemia was identified between the different groups of animals. A significant difference in corneal edema between the groups was found only on day 0. The stage of the AS group was significantly lower than the stage of the EGCG group, while there was no significant difference in the other comparisons. No significant difference was detected in epithelial defects between the groups (Tables 1-4; Fig. 1, Columns: Day 0, 7, 14, and 21).

Table 1. Conjunctival hyperemia (stages)

Rabbit Numbers	Day 0	Day 7	Day 14	Day 21
Group 1				
1	2	1	1	0
2	3	3	3	3
3	3	3	3	3
4*	3	2	1	1
5	1	1	1	0
Group 2				
6	2	2	2	2
7	3	3	3	3
8**	3			
9	3	3	3	3
10	3	3	3	3
Group 3				
11	3	3	3	2
12	3	3	3	3
13	3	3	3	3
14	3	3	3	Phthisis
15	3	2	2	2

*Rabbit number 4 gave birth on the 11th day of the experiment and was not sacrificed at the end of the experiment. **Rabbit number 8 died on the 5th day of the experiment. (0: Normal, 1: Mild, 2: Moderate, 3: Severe).

Table 2. Corneal edema (stages)

Rabbit Numbers	Day 0	Day 7	Day 14	Day 21
Group 1				
1	1	0	0	0
2	3	3	3	3
3	2	2	2	2
4*	2	1	1	1
5	1	0	0	0
Group 2				
6	2	2	2	2
7	3	3	3	3
8**	3			
9	3	3	3	3
10	3	3	3	3
Group 3				
11	3	3	3	3
12	3	3	3	3
13	3	3	3	3
14	3	3	3	Phthisis
15	3	3	3	3

(0: Normal, 1: Mild, 2: Moderate, 3: Severe).

No significant change in conjunctival hyperemia or corneal edema was identified between the pre-treatment and the post-treatment status (day 0 vs. day 21) in any of the groups (Table 5). A significant change in corneal epithelial defect

Table 3. Corneal epithelial defect (stages)

Rabbit Numbers	Day 0	Day 7	Day 14	Day 21
Group 1				
1	1	1	1	0
2	3	3	3	3
3	3	2	2	2
4*	2	2	1	1
5	1	1	0	0
Group 2				
6	2	2	2	2
7	3	3	3	3
8**	3			
9	3	3	3	3
10	3	3	3	3
Group 3				
11	3	3	3	3
12	3	3	3	3
13	3	3	3	3
14	3	3	3	Phthisis
15	3	3	2	2

(0: Normal, 1: Mild, 2: Moderate, 3: Severe).

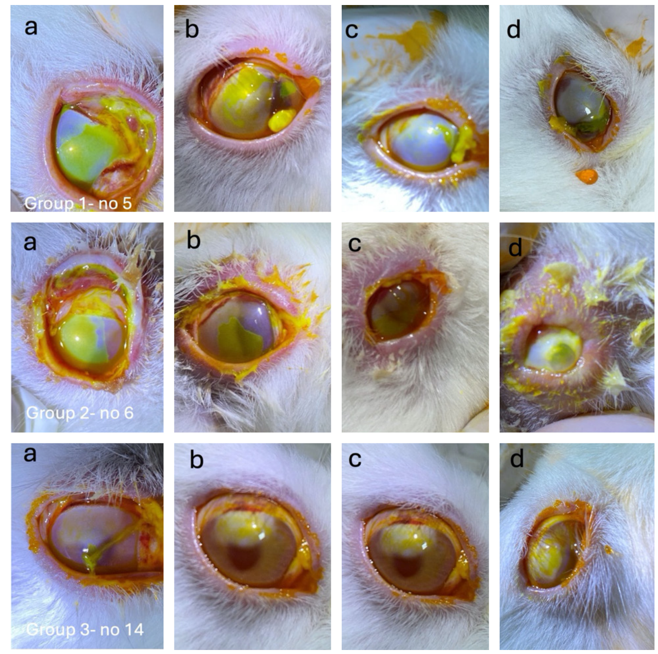

Fig. 1. Clinical examination samples of the different groups.

Table 4. Clinical comparison between groups according to days

	Days			
Clinical status	0	7	14	21
Conjunctival hyperemia	0.291	0.257	0.196	0.312
Corneal edema	0.022	0.25	0.25	0.037
Epithelial defect	0.087	0.029	0.059	0.08

Kruskal Wallis (p:0.025); * Difference between OS and ECGA on day 0: p= 0.032 z: -2.37 (Mann Whitney U; p=0.05).

Table 5. Comparison of pre- and post-treatment clinical status according to agents. (p values)

	Treatment Agents			
Clinical status	ECGA (Group 1)	Resveratrol (Group 2)	AS (Group 3)	Control
Conjunctival hyperemia	0.157	1.0	0.102	1.0
Corneal edema	1.0	1.0	0.083	1.0
Epithelial defect	0.317	1.0	0.046	1.0

Wilcoxon signed ranks (p:0.05).

was found only in the AS group when the pre-treatment and the post-treatment status were compared (day 0 vs. day 21) (Table 5). In conclusion, these clinical results can be interpreted as follows:

- After chemical damage was created, there was significantly less corneal edema in the AS group compared to the EGCG group, while no significant difference was identified in corneal edema between the two groups after 21 days of treatment.
- AS was the only agent that reduced the epithelial defect to a clinically meaningful extent when the pre-treatment status was compared with the post-treatment status within the groups.
- No statistically significant clinical improvement in conjunctival hyperemia and corneal edema was observed with any of the treatments.

Statistical power and sample size analysis were calculated by G-power analysis (Heinrich Heine Universität, Düsseldorf, Germany). It was calculated that the effective sample size could not be reached. Statistical power was 0.5.

2) Histological Examination (Figs. 2, 3):

Hematoxylin & Eosin (H&E)

Normal epithelial cell and stroma morphology were observed in Group 4 (sham). Cell loss in the basal and epithelial regions, occasional erosion of the epithelium, deep stromal edema, inflammatory cell infiltration in the stroma, and swelling in the stroma were observed in the control group. A slight regeneration in the epithelium was observed in Group 1 and Group 3 animals; the regeneration in these groups was more obvious than in Group 2. Stromal edema was found to decrease in all three study groups.

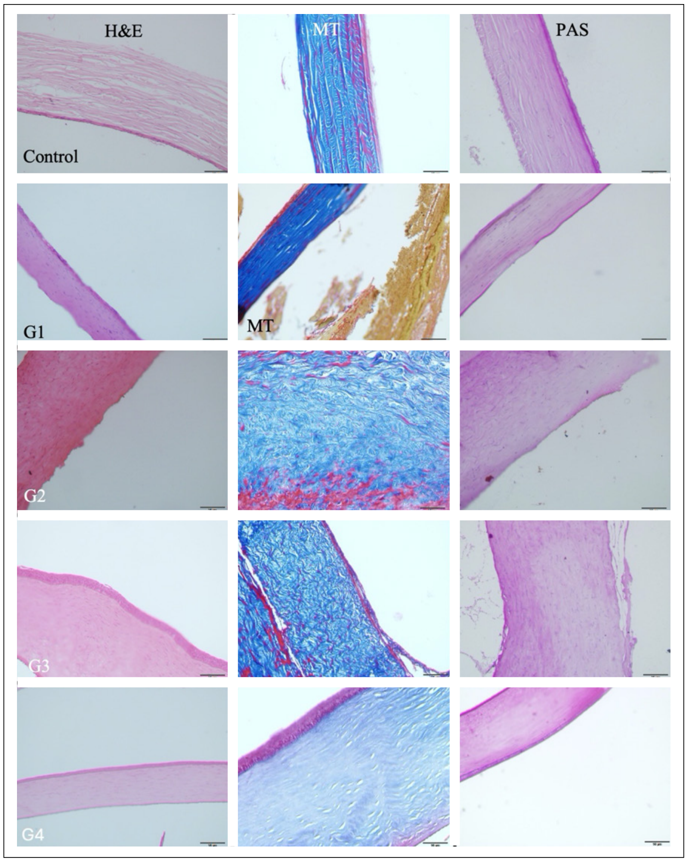

Fig. 2. Histopathological examinations of the study, sham, and control groups with H&E, MT, and PAS.

Periodic Acid–Schiff (PAS) Staining

PAS staining revealed that the Bowman and Descemet membranes were in the form of continuous and homogeneous thick layers in Group 4 but were thinner, albeit heterogeneously, in the control group. An improvement in the thickness and homogeneity of the Bowman and Descemet membranes was observed in all three treatment groups, but was particularly evident in Group 3. These findings were in good agreement with the H&E staining data, supporting the healing of epithelium and stroma in the study groups.

Masson Trichrome (MT)

MT staining indicated a thinning in the stromal collagen fiber thickness in the control group compared to the Group 4 (sham) animals. Although there was no significant difference in collagen fiber thickness between the three treatment groups (Group 1, Group 2, and Group 3), a modest increase in collagen fiber thickness was seen in those groups compared to Group 4.

GFAP Expression

GFAP expression in the stromal cells was determined to be strong in Group 4 and weak in the control group. The level of expression was strong near the middle layers of the cornea in Group 2, while it was moderate in Group 1 and Group 3.

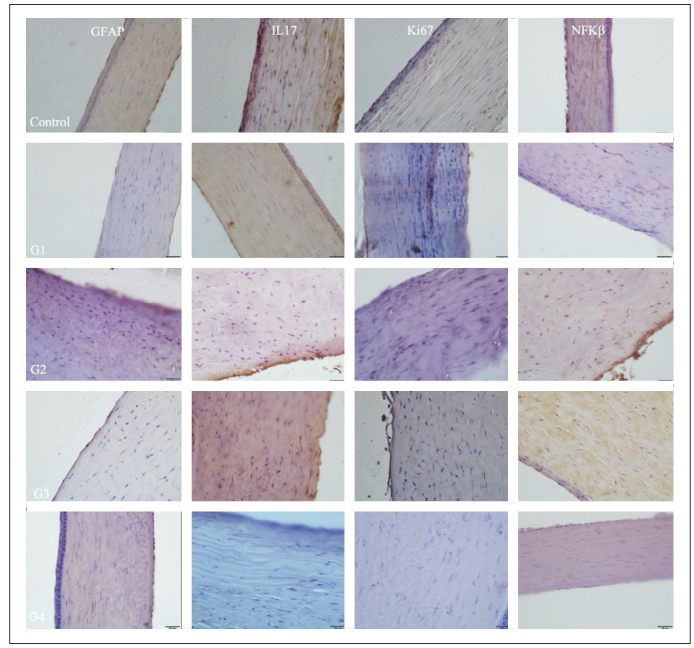

Fig. 3. Histopathological examinations of the study, sham, and control groups with markers such as GFAP, IL-17, Ki-67, and NF-κB.

IL-17 Expression

IL-17 expression was observed to be strong in Group 4 and weak in the control group. The expression was also strong in Group 1 but was determined to be moderate in Group 2 and Group 3.

NF-κB Expression

A strong NF-κB expression was detected in Group 4, while the control group had weak expression. Among the study groups, NF-κB expression level was moderate in Group 2 and Group 3, and strong in Group 1.

Ki-67 Expression

Ki-67 expression was observed to be strong in Group 4 and weak in the control group, while the expression was found to be moderate in Group 1, Group 2, and Group 3.

Discussion

The effectiveness of EGCG and resveratrol in the healing of chemical corneal trauma was evaluated in the current study. AS was accepted as the reference treatment for comparison. We report for the first time a role of resveratrol in the stimulation of neuronal regeneration in the cornea to a greater extent than AS and EGCG. Using immunohistochemical tools, we also report for the first time a role of EGCG in the stimulation of epithelial healing secondary to stromal damage, especially in eyes with stromal edema.

Resveratrol is a hydrophobic compound but has low bioavailability. It is rapidly metabolized if not administered to the patient after peak serum concentrations have been reached. Although its oral and parenteral pharmacokinetics have been studied in detail, its transconjunctival pharmacokinetics have not been studied in detail. Although it is used in high doses in in vitro experiments, it is unclear what benefit the use of solutions above 5–10 µM would provide in in vivo conditions.[15] Epigallocatechin is a hydrophilic molecule with low bioavailability. Esterification, nanoparticle approaches, and silica-based EGCG-NPs are being studied to increase bioavailability. We have not come across any study demonstrating the optimal transconjunctival dose of EGCG. In various pharmacokinetic and corneal injury model studies, it was observed that the effectiveness of solutions containing pure EGCG extract didn't change after the solution concentration increased above 0.1 mg/L and/or 550 mg/kg. However, there is no consensus on the optimal concentration that should be used for eye drop solutions that contain EGCG.[16,17] For these reasons, we prepared the eye drop solutions at the concentrations we specified above.

EGCG is known to have anti-inflammatory, antioxidant, antimutagenic, apoptotic, and anti-neovascular effects.[4,5,7,8] Due to these effects, the compound was recommended for the treatment of both cancer and epithelial damage. However, most reported studies rely on in vitro cell culture rather than clinical research in humans. The number of studies conducted under in vivo conditions is also very few.[7,8,16] Moreover, the studies published to date have not directly compared the efficacy of EGCG with an agent such as AS. In the present study, the effects of both AS and resveratrol were compared with EGCG in a rabbit model of corneal damage. A previous study has reported the effect of EGCG by the extent of corneal neovascularization, while the histological status was investigated by VEGF expression, myeloperoxidase enzyme (MPO), and the infiltration of polymorphonuclear leukocytes.[8] Phosphate buffer was used in the control group. Another study reported the levels of 8-isoprostane and glutathione in the ocular fluid after intragastric administration of green tea extract to mice.[16] However, these authors demonstrated increased oxidative stress in the cornea, contrary to previous studies. In yet another study, EGCG was reported to decrease neovascularization after mechanical stimulation of corneal neovascularization in rabbits.[18] Tseng et al.[19] reported that eye drops mixed with green tea extract were more effective in reducing eye dryness. In the current study, EGCG was found to increase IL-17, NF-κB, and GFAP expression and decrease stromal edema.

Several different markers for inflammation, proliferation, and neuronal regeneration were used in the current study. IL-17 and NF-κB are among the main inflammatory cytokines of the innate immune system. IL-17 plays a crucial role in the bridge between the innate immune system and the activation of the adaptive immune system.[20-22] Although IL-17 is generally expressed throughout the body, it essentially executes an important role in epithelial cells.[20] NF-κB activation has been reported to induce corneal regeneration.[23,24] GFAP is produced extensively in neuroglial cells and also functions as a marker for neural stem cells.[25,26] Therefore, GFAP has been used extensively as a marker for the healing of the optic nerve, retina, as well as corneal damage.[27-29] Ki-67 is a proliferation marker that reflects corneal epithelial and limbic proliferation, as well as endothelial healing.[30-32]

Overall, the current study illuminated that AS was superior to EGCG and resveratrol for clinical healing of the cornea after chemical trauma. However, EGCG showed a strong effect on stromal healing histologically, while resveratrol could stimulate neuronal regeneration. Previous studies have shown that resveratrol can stimulate neural regeneration in ischemic neuronal damage and neurodegenerative diseases.[33,34] Additionally, it has been observed that resveratrol causes a decrease in ischemic damage in the retina and has neuroprotective effects on retinal ganglion cell dendrites.[35,36] In our study, the histologically positive effects of resveratrol on corneal neuronal regeneration support those neuroprotective findings. Previous studies have shown that EGCG causes a decrease in dry eye symptoms and a decrease in corneal neovascularization after corneal injury.[8,18] In addition, our study has shown that it causes a histological decrease in corneal edema. In light of our findings, more studies are needed to compare the efficacy of EGCG with treatments with proven effectiveness. The current study meets this need, albeit at a preliminary level.

In our study, a more up-to-date staging system that evaluates acute chemical corneal damage was used, which has not been used in other studies investigating the effects of EGCG. In addition, a wider variety of histological and immunochemical markers were used in our study, especially for neuronal regeneration and innate immune response, than those used in other animal studies investigating the effects of EGCG to date.

Experiments in humans have a strong ethical burden. Nonetheless, pharmacologically effective drug forms can be developed with studies including a larger number of cases. Based on the findings of the current study, EGCG and resveratrol can be considered as supplement agents to the agents that are already in use for ocular surface chemical injuries, especially for corneal edema and corneal neuronal damage, respectively.

Limitations

The limitations of the present study are the relatively small sample size, limited number of markers evaluated with immunohistochemical staining, and the relatively short follow-up period. Additionally, frequently used drugs such as anti-VEGF agents, curcumin, apigenin, etc., could also be evaluated in a comparative study of potential treatment agents. Many of these limitations have arisen primarily due to budgetary constraints.

Conclusion

Resveratrol could stimulate neuronal regeneration histologically in the cornea to a greater extent than AS and EGCG after chemical trauma. EGCG can heal corneal edema when tissues are examined histologically.

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Ethics Committee Approval: The Ege University Animal Experiments Ethics Committee granted approval for this study (date: 19.06.2019, number: 2018/130).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: O.B.S., M.P.; Design: Y.C., M.P.; Supervision: O.B.S., M.P.; Resource: F.O., E.H.G.; Materials: Y.C., S.Y., A.B., F.O., E.H.G.; Data Collection and/or Processing: Y.C., S.Y.; Analysis and/or Interpretation: Y.C., C.D., A.B., E.H.G.; Literature Search: Y.C.; Writing: Y.C.; Critical Reviews: M.P.

Conflict of Interest: None declared

Use of AI for Writing Assistance: Not declared.

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