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Dietary Nitrate Supplementation in Sport: Sources and Factors Influencing Ergogenic Effects- A Narrative Review

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Abstract

Dietary nitrate supplementation has gained considerable attention as a potential ergogenic aid due to its ability to enhance nitric oxide bioavailability through the nitrate-nitrite-nitric oxide pathway. Increased nitric oxide availability may improve vascular function, mitochondrial efficiency, skeletal muscle contractility, and exercise economy, potentially enhancing exercise performance. This narrative review summarizes current evidence regarding the physiological mechanisms, dietary sources, supplementation protocols, and ergogenic effects of dietary nitrate supplementation in sport. Evidence indicates that nitrate supplementation may improve exercise economy, endurance capacity, and high-intensity exercise performance, particularly in recreationally active and moderately trained individuals. Emerging evidence also suggests potential benefits during resistance exercise and repeated sprint activities. However, the ergogenic response to nitrate supplementation appears to be highly variable and influenced by factors including training status, sex, habitual diet, oral microbiota composition, genetic polymorphisms, environmental conditions, and supplementation strategy. Current evidence further suggests that nitrate supplementation provides limited benefits in elite endurance athletes, women, and under hypoxic conditions. Acute ingestion of approximately 350-500 mg nitrate consumed 2-3 hours before exercise appears to represent the most effective supplementation strategy. Overall, dietary nitrate supplementation may provide ergogenic benefits under specific conditions; however, substantial inter-individual variability remains, and further research is required to develop personalized supplementation approaches.

Keywords

beet or beetroot, nitrate, supplementation, sport nutrition, nitrates, hypobaric hypoxia

1. Mechanism of Action of Dietary Nitrates and Nitric Oxide in the Human Body

Dietary nitrate (NO_3^-) has gained attention in sport physiology due to its ability to increase nitric oxide (NO) bioavailability through an alternative pathway to the classical nitric oxide synthase NOS-dependent system. This so-called nitrate-nitrite-NO pathway represents a complementary mechanism for NO production.

After ingestion, dietary nitrate is rapidly absorbed in the upper gastrointestinal tract and enters systemic circulation. Approximately 25% of circulating nitrate is actively taken up by the salivary glands and concentrated in saliva[1]. Oral commensal bacteria then reduce nitrate (NO_3^-) to nitrite (NO_2^-) via nitrate reductase enzymes. Upon swallowing, nitrite can be further reduced to nitric oxide (NO) in the acidic environment of the stomach or in peripheral tissues.

1.1 Classical NOS-dependent vs nitrate-dependent NO production

Traditionally, NO is synthesized endogenously from L-arginine via nitric oxide synthase (NOS) enzyme. The enzyme has three isoforms: endothelial (eNOS), neuronal (nNOS) and inducible (iNOS). eNOS and nNOS are constitutively expressed, whereas iNOS is mainly expressed in macrophages and is induced by inflammatory stimuli[2] . The NOS-dependent pathway requires oxygen for nitric oxide synthesis and may therefore become less effective during hypoxia, acidosis, or oxidative stress. In contrast, the nitrate-nitrite-NO pathway is oxygen-independent, partially dependent on oral and gastrointestinal microbiota for nitrate reduction, and is enhanced under the hypoxic and acidic conditions characteristic of exercising skeletal muscle, making it particularly relevant during muscular work[3,4].

1.2 Role of oral microbiota

A critical step in nitrate metabolism is the reduction of nitrate to nitrite by facultative anaerobic bacteria located in the oral cavity. This step is essential, as mammals lack significant nitrate reductase activity[5] . This microbial contribution introduces inter-individual variability in nitrate responsiveness, as oral bacterial composition can differ substantially between individuals[6] . The importance of oral microbiota has been demonstrated in studies showing that antibacterial mouthwash can significantly reduce plasma nitrite levels and attenuate the physiological effects of dietary nitrate supplementation. Moreover, dietary nitrate intake has been shown to increase oral health-associated bacterial genera while reducing bacteria implicated in oral diseases[7,8].

2. Physiological effects of increased NO availability

Once nitrite enters the systemic circulation, it can be reduced to NO through several complementary pathways. The predominant mechanism appears to be nitrite reduction by deoxyhemoglobin , as its nitrite reductase activity increases with declining oxygen saturation[9], thereby facilitating localized NO production in metabolically active tissues such as exercising skeletal muscle. Additional NO generation may occur via xanthine oxidoreductase-mediated reduction and through non-enzymatic conversion under acidic conditions, particularly during intense exercise when tissue oxygen tension and pH are reduced[9].

Increased NO bioavailability leads to several systemic and muscular effects relevant to exercise performance:

- Nitric oxide enhances blood flow to active skeletal muscle by activating soluble guanylate cyclase (sGC), increasing intracellular cyclic guanosine monophosphate (cGMP) levels, and promoting vascular smooth muscle relaxation and vasodilation[10].

- Improved mitochondrial efficiency is characterized by enhanced oxidative phosphorylation coupling and reduced fatty acid-dependent proton leak during basal and submaximal mitochondrial respiration. Proposed mechanisms include NO-mediated modulation of mitochondrial proteins involved in proton conductance, particularly adenine nucleotide translocase (ANT) and uncoupling proteins, which may decrease uncoupled respiration and improve mitochondrial coupling efficiency[11].
- Increased nitric oxide bioavailability may improve skeletal muscle function by altering excitation-contraction coupling and intracellular Ca^{2+} kinetics. Proposed mechanisms include NO-mediated nitrosylation of ryanodine receptors, leading to enhanced sarcoplasmic reticulum Ca^{2+} release, as well as increased signaling through the sGC-cGMP-PKG pathway (PKG- protein kinase G), which may augment myofilament Ca^{2+} sensitivity and optimize force generation during muscle contraction[9] .

These effects collectively contribute to improved exercise economy and, in some cases, enhanced high-intensity exercise performance.

3 Effects of Dietary Nitrate Supplementation on Exercise Performance

The ergogenic effects of nitrate are primarily attributed to increased nitric oxide bioavailability, which may improve vascular function, mitochondrial efficiency, muscle contractility, and exercise economy. Current evidence suggests that the magnitude of performance enhancement depends on exercise modality, supplementation protocol, training status, and environmental conditions such as hypoxia.

3.1 Exercise Economy and Oxygen Cost of Exercise

One of the most consistent findings in the literature is that dietary nitrate supplementation reduces the oxygen cost of submaximal exercise. Investigations demonstrated that nitrate ingestion decreases whole-body VO_2 during steady-state exercise without reducing external work output [12], indicating improved exercise economy. Proposed mechanisms include enhanced mitochondrial oxidative phosphorylation efficiency, reduced ATP cost of muscle force production, and improved muscle perfusion[10,11].

3.2 Endurance Exercise Performance

Dietary nitrate supplementation has been most extensively studied in endurance exercise. Multiple systematic reviews and meta-analyses report improvements in time-to-exhaustion performance[12,13] (duration during which an athlete is able to continue exercise before reaching volitional exhaustion). Recent meta-analyses indicate that nitrate supplementation is associated with beneficial effects on endurance exercise performance, particularly during exercise lasting approximately 2-10 minutes[14]. Positive effects have been observed in cycling, running, rowing, and swimming protocols [12]. However, there is no clear evidence that nitrate supplementation enhances time-trial performance [12,13], which is assessed by shortening the time required to complete a predetermined distance or amount of work which is especially important in endurance sport competition. In addition to endurance exercise, increasing attention has been directed toward the potential effects of nitrate supplementation during resistance and high-intensity exercise.

3.3 Strength and Power Performance

There is growing evidence that, in addition to its established benefits for endurance performance, nitrate supplementation may also positively influence resistance training performance. However, compared with endurance exercise, research investigating the effects of nitrate supplementation in strength-based sports remains relatively limited. A recent review reported that nitrate supplementation administered in doses commonly used in endurance sports (approximately 400 mg consumed 2-3 hours before exercise) may enhance muscle strength and power output during resistance exercise performance [15]. These findings are supported by another review demonstrating improvements in several variables associated with explosive resistance exercise following nitrate supplementation [16]. Reported benefits included increased peak power during squat exercise, enhanced isokinetic knee flexion and extension performance, and improved bench press performance, including greater contraction velocity. Furthermore, nitrate supplementation was associated with greater total work output and improved repeated sprint performance during high-intensity exercise protocols [16]. Collectively, findings indicate that dietary nitrate supplementation may be effective in enhancing power production and movement velocity during explosive resistance training and sprint-type activities.

In addition, evidence from team-sport research indicates that short-term nitrate supplementation protocols involving repeated nitrate intake in the days preceding exercise may further enhance performance during high-intensity intermittent activities that require repeated sprint efforts[17]. These findings suggest that nitrate supplementation may be particularly beneficial in sports characterized by explosive movements, rapid changes in intensity, and repeated bouts of high-intensity exercise.

3.4 VO_2max

Evidence indicates that nitrate supplementation can positively affect VO_2max, although the magnitude of improvement is often small and depends on training status, dosage, and supplementation duration. A review reported that beetroot juice supplementation significantly improved VO_2max in healthy adults, although the overall effect size was small [18]. Some studies have reported more pronounced improvements in VO_2max following beetroot juice supplementation [19,20]; however, many of these investigations were conducted on relatively small sample sizes, which may limit the generalizability of these findings. Nevertheless, the majority of current evidence suggests that dietary nitrate supplementation does not substantially influence VO_2max, despite its potential beneficial effects on exercise economy and oxygen utilization during submaximal exercise[12,13].

4. Forms, dose, and timing of dietary nitrate supplementation

Dietary nitrate can be provided through nitrate-rich foods, especially beetroot and green leafy vegetables, beetroot juice or concentrated beetroot shots, beetroot-based powders, and inorganic nitrate salts such as sodium nitrate. In sport research, beetroot juice is the most commonly used form because it provides a relatively standardized and practical nitrate dose, although nitrate content may vary between commercial products and natural foods. Fresh beetroot may provide higher nitrate and antioxidant content than many beetroot-based dietary supplements[21,22].

Most studies use an acute nitrate dose of approximately 6-12 mmol NO_3^- consumed 2-3 hours before exercise[13,23], which corresponds to the time required for plasma nitrite concentrations to peak after ingestion [14]. The greatest ergogenic effects appear to be achieved with acute nitrate doses ranging from 5 to 14.9 mmol, with additional benefits observed at the higher end of this range, whereas chronic supplementation generally requires approximately 5-10 mmol of nitrate per day[14]. Therefore, for athletes, a practical supplementation strategy is usually 6-8 mmol NO_3^-, equivalent to approximately 350-500 mg nitrate, consumed 2-3 hours before training or competition.

4.1 Vegetables richest in nitrate

The vegetables with the highest nitrate content are generally green leafy and root vegetables. Vegetables belonging to the Brassicaceae family, such as rocket (recognized as the highest nitrate-accumulating vegetable[24]), radish, and mustard, as well as the Amaranthaceae family, including beetroot and spinach, exhibit a particularly strong tendency to accumulate nitrate. In beetroot, nitrate concentrations are generally highest in the periderm (peel)[25].

The degree of nitrate accumulation differs substantially between vegetable species and plant tissues[25]. Leafy vegetables generally contain higher nitrate concentrations than fruit vegetables, whereas root vegetables exhibit intermediate nitrate accumulation [24]. Importantly, nitrate concentration may vary markedly depending on plant variety, environmental conditions, light exposure, fertilizer use, season, storage conditions, and harvest timing. For example, reduced light exposure and nitrogen fertilization substantially increase nitrate accumulation in vegetables [24,26].

4.2 Nitrate concentration in beetroot supplements and juices

Considerable variability exists in the nitrate content of commercial beetroot juices and dietary supplements, which may substantially influence their ergogenic potential. Analyses of commercially available beetroot products have demonstrated large differences in nitrate concentration both between manufacturers and between production batches of the same product. Studies reported an approximately 50-fold difference in nitrate content among commercially available beetroot juice products marketed to athletes, with only a small proportion consistently providing the ≥5 mmol NO_3^- dose generally considered necessary to enhance exercise performance [27].

Concentrated beetroot “shots” and standardized sport supplements generally contain the highest nitrate concentrations (~6,3 mg/mL[28]), commonly providing approximately 5-8 mmol nitrate in 70 mL servings[29]. In contrast, non-concentrated beetroot juices and many beetroot-based dietary supplements often contain substantially lower and more variable nitrate levels[21,28]; consequently, approximately 250 mL of fresh beetroot juice (nitrate concentration ~1.4 mg/mL[28]) may be required to provide the minimum effective nitrate dose (~350 mg) necessary to elicit ergogenic effects.

Season, storage conditions, processing methods, and product formulation appear to strongly influence nitrate stability. Nitrate concentrations in beetroot juices were lower during some storage periods and nitrate degradation was accelerated at room temperature, whereas refrigerated storage preserved nitrate content[28].

Fermentation may additionally alter nitrate and nitrite concentrations in beetroot products. During fermentation, nitrate levels generally decrease because of microbial nitrate reduction and assimilation processes, while nitrite concentrations may transiently increase as intermediate products of nitrate metabolism. However, as fermentation progresses and pH declines, nitrite levels subsequently decrease to low concentrations[30].

5. Inter-Individual Variability in Response

Considerable inter-individual variability exists in the physiological and performance responses to dietary nitrate supplementation. Factors influencing nitrate responsiveness may include oral microbiota composition, habitual diet, sex, age, genetic polymorphisms, fitness level, and baseline NO availability.

5.1 Fitness level

Improvements are generally more pronounced in recreationally active or moderately trained individuals than in elite endurance athletes, possibly because highly trained athletes already exhibit elevated endogenous nitric oxide production due to greater dietary nitrate intake-potentially associated with substantially higher energy intake, which may be up to 100% greater than that of non-athletes- and enhanced eNOS/nNOS-dependent NO synthesis capacity[31].

Some evidence suggests that nitrate supplementation may exert greater physiological effects in type II (fast-twitch) muscle fibers because these fibers operate under lower oxygen tension compared with type I (slow-twitch) fibers, conditions that favor nitrite reduction to nitric oxide[32,33]. Since elite endurance athletes generally possess a lower proportion of type II muscle fibers, this muscle phenotype may partly explain the attenuated ergogenic response to nitrate supplementation frequently observed in highly trained populations [33]. Furtheremore, polymorphisms in the eNOS gene (NOS3) may be associated with superior endurance performance, with certain NOS3 variants occurring more frequently in elite endurance athletes[34,35]. The physiological significance of these polymorphisms remains unclear; however, they may contribute to the reduced ergogenic response to nitrate supplementation often observed in highly trained athletes.

5.2 Sex

Most studies investigating dietary nitrate supplementation have predominantly involved male participants, resulting in a substantial underrepresentation of female athletes in the current literature[13,36]. Consequently, the effects of nitrate supplementation in women have not yet been adequately examined. Based on the limited available evidence, meta-analyses have generally not demonstrated significant ergogenic or endurance-enhancing effects of nitrate supplementation in female athletes[36]. One study directly compared males and females regarding the effects of nitrate supplementation on steady-state VO_2 reduction and prolongation of time-to-exhaustion- well-established ergogenic outcomes previously reported in the literature. The authors observed significant improvements in exercise economy and endurance capacity in males following nitrate supplementation, whereas no beneficial effects were detected in females [34]. A recent meta-analysis reported that nitrate supplementation in women may modestly improve explosive power, particularly countermovement jump height; however, its effects on muscle strength and sprint performance appear limited and generally not statistically significant [37]. Poredoš et al. applied the same experimental protocol to both men and women to assess isometric knee extensor strength following nitrate supplementation. While no significant improvements in muscle strength were observed in either sex, endurance performance was significantly enhanced only in men. In contrast, women did not appear to benefit from nitrate supplementation in either strength or endurance outcomes[38].Although these findings are based on relatively small sample sizes, they suggest that sex may influence the physiological response to dietary nitrate supplementation. Therefore, further well-controlled studies involving female athletes are needed to better understand potential sex-specific effects of nitrate supplementation on exercise performance. Moreover, nitric oxide (NO) plays an important role in the reproductive system, and its bioavailability may be influenced by hormonal fluctuations. During the follicular phase of the menstrual cycle, estrogen upregulates NO production, whereas progesterone, which increases during the luteal phase, may downregulate NO levels[39]. Despite the potential interaction between nitrate supplementation and hormonal fluctuations, a study using a moderate-intensity time-to-exhaustion protocol in non-aerobically trained young women- a population and exercise model considered highly responsive to nitrate supplementation in men- reported not only a lack of ergogenic effect, but even a reduction in time-to-exhaustion performance, regardless of menstrual cycle phase[40]. Similarly, another study reported no significant improvements in muscle strength following nitrate supplementation across different phases of the menstrual cycle, further suggesting limited ergogenic effects of nitrate supplementation in women [41]. Overall, the existing data demonstrate that dietary nitrate supplementation provides limited or no consistent ergogenic benefits in women, indicating that physiological responses to nitrate supplementation differ substantially between sexes.

5.3 Habitual diet

Basal dietary nitrate intake may differ substantially between individuals and depends on factors such as habitual dietary patterns, seasonal variability, and total energy intake. Variability in nitrate concentrations among vegetables further complicates the estimation of dietary nitrate intake. Seasonal and environmental conditions strongly influence nitrate accumulation in plants. During winter, increased fertilizer application often promotes higher nitrate accumulation in vegetable tissues [28]. In contrast, organically grown vegetables, in which synthetic fertilizers are not used, generally exhibit lower nitrate concentrations during winter seasons [28]. Considering the well-established upper range at which nitrate supplementation appears to exert ergogenic benefits (approximately 15 mmol per dose)[14], it may be assumed that individuals with already high dietary nitrate intake derive limited additional benefit from supplementation. Moreover, excessive nitrate intake may potentially pose a risk of toxicity. The World Health Organization (WHO) established the Acceptable Daily Intake (ADI) for nitrate in the 1990s at <3.7 mg/kg body weight/day [42]. This threshold appears relatively low compared with the nitrate doses commonly used in ergogenic supplementation studies, many of which substantially exceed the ADI. The estimated lethal dose of nitrate in humans is approximately 330 mg/kg body weight [42]. Nevertheless, epidemiological evidence does not suggest that dietary nitrate intake is associated with an increased risk of cancer or methemoglobinemia in adults, and nitrate derived from vegetables is generally considered safe [42].

5.4 Age

Evidence indicates that aging is associated with reduced nitric oxide bioavailability, as reflected by lower plasma nitrite and FeNO (Fractional concentration of Exhaled Nitric Oxide) observed in older individuals [43]. The majority of studies investigating dietary nitrate supplementation have used young athletes (<30 years old) as experimental models. However, one review analyzing 12 studies involving males and females aged approximately 60 years and older demonstrated that nitrate supplementation may also exert ergogenic effects in older populations. Additionally, nitrate intake was associated with beneficial cardiovascular effects, including reduced blood pressure and increased cerebral blood flow[44]. Therefore, in elderly individuals, dietary nitrate supplementation may provide benefits not only for exercise performance, which is often not the primary objective in this population, but also as a supportive strategy for age-related cardiovascular and functional impairments.

Future research should therefore focus on personalized approaches to nitrate supplementation and on identifying factors contributing to inter-individual variability in supplementation responses, as the numerous factors influencing nitrate supplementation effectiveness may partly explain the equivocal ergogenic effects reported across studies.

6. Synergistic effect of L-Arginine and Nitrate Supplementation

Few studies have investigated whether combining nitrate and L-arginine supplementation produces additive ergogenic effects compared with either supplement alone. Kavcı et al. conducted a double-blind, randomized crossover study in 15 elite taekwondo athletes examining the effects of nitrate supplementation, L-arginine supplementation, combined nitrate and L-arginine intake , and placebo on aerobic and anaerobic performance, agility, balance, and fatigue-related variables. Nitrate was provided via spinach-derived nitrate, whereas L-arginine was administered as a 6 g oral dose three hours before exercise [45].

The combined nitrate and L-arginine supplementation produced the greatest improvements in peak and mean anaerobic power, agility performance, and post-exercise lactate responses compared with placebo. In contrast, nitrate or L-arginine supplementation alone produced smaller and less consistent effects [45].

However, evidence from studies conducted in elite endurance athletes also suggests limited additive effects of combined nitrate and L-arginine supplementation. In a randomized crossover study involving elite cross-country skiers, co-supplementation with nitrate and L-arginine increased plasma nitrate and nitrite concentrations compared with placebo; Nevertheless, these physiological changes did not consistently translate into superior exercise performance outcomes relative to nitrate supplementation alone[46]. These findings may suggest that although combined supplementation may augment NO precursor availability, there is currently insufficient evidence to conclude that L-arginine provides meaningful synergistic ergogenic effects when administered alongside dietary nitrate. Further research involving recreationally active and moderately trained individuals is necessary, as available evidence indicates that these populations may exhibit greater responsiveness to dietary nitrate supplementation than highly trained endurance athletes.

7. Nitrate supplementation in hypoxic environment

The physiological basis of the nitrate-nitrite-nitric oxide pathway suggests that the ergogenic effects of nitrate supplementation may be enhanced under hypoxic conditions compared with normoxic environments. Indeed, nitric oxide bioavailability appears to increase as part of the physiological adaptation to high altitude. Interestingly, high-altitude populations such as Tibetans paradoxically exhibit lower hemoglobin concentrations compared with lowland populations, while simultaneously demonstrating significantly greater nitric oxide production and bioavailability[16]. Moreover, Tibetan high-altitude natives demonstrate a lower oxygen cost of exercise, a physiological response similar to that reported following dietary nitrate supplementation. Notably, this adaptation is not consistently observed in lowlanders acclimatized to altitude, despite evidence of elevated nitric oxide levels [16]. Collectively, these findings suggest that although enhanced nitric oxide bioavailability plays an important role in physiological adaptation to hypoxia, it may not necessarily result in additional ergogenic benefits during exercise performance at high altitude.

Recent evidence investigating nitrate supplementation under hypoxic and high-altitude conditions suggests that its ergogenic potential may be limited. A recent meta-analysis of nine randomized controlled trials demonstrated that although nitrate supplementation significantly increased nitric oxide-related biomarkers, it did not improve VO_2max, oxygen saturation, heart rate, or perceived exertion during exercise at altitude. These findings suggest that enhanced nitric oxide bioavailability under hypoxic conditions does not necessarily translate into improved exercise performance or cardiopulmonary fitness at high altitude [47]. Studies employing nitrate supplementation protocols similar to those previously shown to improve performance and exercise oxygen economy under normoxic conditions did not demonstrate significant improvements in endurance performance or exercise economy during hypoxic exposure[48,49].

Several studies reported substantial increases in nitric oxide-related biomarkers following nitrate supplementation under hypoxic conditions without corresponding improvements in exercise performance. For example, acute sodium nitrate supplementation increased plasma nitrate concentrations approximately tenfold during hypobaric hypoxia, yet no significant improvements were observed in forearm blood flow, tissue oxygenation, or exercise capacity at simulated altitude[49]. Similarly, chronic beetroot juice supplementation during six weeks of intermittent hypoxic endurance training did not enhance VO_2max, lactate threshold, or time-trial performance beyond the adaptations induced by hypoxic training alone [50]. Overall, current evidence suggests that nitrate supplementation during high-altitude exposure does not provide consistent ergogenic benefits and therefore may not be effective for enhancing acclimatization or improving exercise tolerance at altitude. The limited effects observed in hypoxic environments may be further explained by the fact that altitude training protocols are typically utilized by highly trained athletes with already elevated aerobic capacity, a population that has generally been shown to exhibit a reduced responsiveness to nitrate supplementation.

8. Discussion

Current evidence indicates that dietary nitrate supplementation may exert ergogenic effects through improvements in exercise economy, endurance capacity, and high-intensity exercise performance. However, despite the large number of studies investigating nitrate supplementation, considerable discrepancies in findings remain, and the factors underlying inter-individual variability are not yet fully understood. Based on the available literature, the most effective supplementation strategy appears to involve acute ingestion of approximately 350-500 mg of nitrate consumed 2-3 hours before exercise.

The ergogenic effects of nitrate supplementation appear to be most pronounced in recreationally active or moderately trained males performing exercise under normoxic conditions. Nevertheless, numerous factors may attenuate these benefits, including low nitrate content in supplements, inappropriate timing of ingestion, use of antibacterial mouthwash, habitual dietary nitrate intake, and individual physiological characteristics such as fitness level, sex, and oral microbiota composition. Consequently, future research should focus on personalized approaches to nitrate supplementation and on identifying the mechanisms responsible for the considerable variability in ergogenic responsiveness observed between individuals.

Disclosure Section

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Conceptualization, B.K., M.K. and M.G.; methodology, K. G.-M.; validation, M.B.; investigation K.G.-M., Z.M., K.P., H.P., M.Z. and J.B.; writing—original draft, H.P., M.Z., J.B., Z.M., K.P., M.K. and M.G.; writing—review and editing, B.K. and M.B.; project administration, B.K.; All authors have read and agreed to the published version of the manuscript.

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