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*Review Article*

# The Influence of β-Alanine Supplementation on Recovery Biomarkers in Adults: A Systematic Review and Meta-Analysis

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**Abstract**

***Background:*** Clinical studies, investigating the effect of β-Alanine (BA) supplementation on recovery biomarkers in physically active individuals, have generated inconsistent results. This systematic review and meta-analysis study aimed to clarify the clinically relevant dietary effects of BA supplementation.

***Methods:*** A comprehensive search was done in the electronic databases of Scopus, PubMed, ISI Web of Science and Embase from inception to 2022. Meta-analysis was done using the random-effects model. Pooled effect size was evaluated using standard mean difference (SMD) and 95% confidence intervals (CI). Heterogeneity of between-study was evaluated according to Cochran's Q test and $I^2$. Subgroup analysis was conducted to identify the potential sources of heterogeneity.

***Results:*** Overall, 32 studies were included in the current study. The results suggested that BA supplementation increases carnosine level significantly (SMD: 0.22mmol/L, 95%CI: -0.17, 0.61, P=0.27) but no effect was shown about lactate, fatigue, $VO_2$, pH and bicarbonate ($HCO_3^-$) (P>0.05). Subgroup analysis revealed a significant association of VO2, carnosine and fatigue with supplementation dosage, gender and duration of administration respectively.

***Conclusion:*** BA supplementation emerged its beneficial effects on enhancing carnosine level which highlights its ergogenic effects. In contrast, no significant effects had been shown in term of fatigue delay and blood levels of lactate, $HCO_3^-$, pH, and $VO_2$ value. These results warrant more investigation in a prospective design to clarify the exact mechanism in this way.

## Introduction

Several approaches have been considered for maximizing recovery in active people. Evidence indicate that intensive exercise contribute to conversion of lactic acid to lactate and increased level of hydrogen cation ($H^+$). This reaction is accompanied with a decline in the pH and acidosis.[1,2] Accordingly, previous studies illustrated that acidosis may disrupt several metabolic processes including: glycolysis, muscle contraction system and re-synthesis of phosphorylcreatine which eventually leads to fatigue and reduced force production.[3,4] In this regard, importance of buffers which resists to pH changes cannot be ignored. Likewise, proper nutritional intervention may exert its favorable effects and β-alanine (BA) is a valuable supplement which overcome acidosis in this sense. BA, as a non-essential amino acid is synthesized in the liver and supplied through diet and endogenous synthesis.[5] It is found in animal foods such as beef, poultry and fish in a large amount.[6] Also, degradation of pyrimidine in thymine, cytosine and uracil results in endogenous synthesis of BA and its transport to skeletal muscle is dependent on sodium and chloride.[7,8] Moreover, BA known as a rate limiting precursor of carnosine (β-alanyl-l-histidine) in skeletal muscle.[4,9] Despite several physicochemical buffers in muscle, imidazole ring in the carnosine ($pK_a$ = 6.83) makes it as one of the potent intracellular buffer.[10,11] So this cytoplasmic dipeptide may compensate the acidosis caused by intensive exercise and delay the onset of fatigue.[5,12] Prior studies demonstrated that BA supplementation could cause carnosine decline about 40-80 percent. On the other hand, lactate concentration is correlated with $H^+$ ion accumulation, so proton gradient and pH maintenance may help to attenuate fatigue.[13,14] Therefore, a strategy to attenuate the fatigue doubles the importance of BA

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supplementation. So its unique features became the focus of attention and attracted our interest to evaluate its effects on recovery biomarkers. In addition, controversial results about BA effects and several studies with different protocols prompted us to conduct a comprehensive and quantitative study as a systematic review and meta-analysis to ensure its impact on recovery markers among adults. Therefore, feeling the need to conduct such a study will shed light about its impact.

## Materials and Methods

### *Search strategy*

The current systematic review and meta-analysis was conducted according to PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) guideline.[15] A comprehensive systematic search was performed in Scopus, PubMed, ISI Web of Science and Embase electronic databases and Google Scholar for randomized, placebo-controlled trials investigating the effect of BA supplementation on recovery biomarkers from inception to 2022. The following keywords were used: "β-alanine" [Title/Abstract]) OR " β-alanine " [Title/Abstract]) OR "Beta-alanine" [Title/Abstract]) OR " Beta-alanine " [Title/Abstract]) AND ("recovery" [Title/Abstract]) OR ("lactate" [Title/Abstract]) OR ("$VO_2$"[Title/Abstract]) OR ("carnosine"[Title/Abstract]) OR ("pH" [Title/Abstract])) OR ("fatigue" [Title/Abstract]) OR ("$HCO_3$" [Title/Abstract])) OR ("recovery" [Mesh]) OR "lactate"[Mesh]) OR "$VO_2$"[Mesh]) OR "carnosine"[Mesh]) OR "pH"[Mesh]) OR "fatigue"[Mesh]) OR "$HCO_3$"[Mesh]) AND (randomized controlled trial[Publication Type]) OR controlled clinical trial[Publication Type]) OR "clinical trial"[Title/Abstract]) OR random*[Title/Abstract]) OR supplementation[Title/Abstract]) OR placebo[Title/Abstract]) OR groups[Title/Abstract]) OR trial[Title/Abstract]) OR "randomized controlled trial"[Title/Abstract]) OR "controlled clinical trial"[Title/Abstract]) NOT ("mouse"[Title/Abstract]) OR "rat"[Title/Abstract]) OR "rats"[Title/Abstract]) OR "mice"[Title/Abstract]) OR rabbit*[Title/Abstract]) OR hamster*[Title/Abstract]) OR chicken*[Title/Abstract]) OR broiler*[Title/Abstract]) OR animal[Title/Abstract]) OR "in vivo"[Title/Abstract]) OR "in vitro"[Title/Abstract]). Hand-searching was performed using reference and citation lists of all previous review articles to include all relevant and eligible trials. No language limitation was applied in the search process.

### *Study selection*

The inclusion criteria in the present study was as following: 1) studies used BA supplementation as an intervention in the physically active individuals; 2) studies reported lactate, carnosine, $VO_2$, fatigue and $HCO_3^-$ at baseline and after intervention as mean and standard deviation (SD) in both treatment and placebo groups; 3) conducted as a randomized placebo-controlled trials. Also, studies with no placebo group, reviews, *in-vitro* and *in-vivo* studies, concomitant intervention with other ingredients and lack of data about baseline or end trial markers or SD value and studies conducted among pregnant and lactating women were excluded from the study.

### *Data extraction*

Two independent researchers (MM and MZ) screened the full text of eligible articles independently and discussed about all disagreements. Afterward, the following characteristics were extracted: first author of the study, year of publication, publisher journal, study region, study population, number of enrolled participants, gender of participants, mean age, intervention dosage and duration, mean and SD of lactate, carnosine, $VO_2$, pH, fatigue and $HCO_3^-$ in supplement and placebo groups before and after intervention.

### *Quality assessment*

Included studies were assessed and qualified by Cochrane Collaboration's scale.[16] The evaluation was done according to following items: sequence generation sufficiency, allocation concealment blinding, selective outcome reporting, elucidating of dropouts and other possible causes of bias and studies were assigned as high risk of bias, low risk of bias, and unclear.

### *Statistical analyses*

Stata 16 (Stata Corporation, TX) was used for the statistical analysis to conduct random-effect model. The effect size was represented as standard mean difference (SMD) and 95% confidence interval (CI). Cochrane's Q test and $I^2$ tests were performed to investigate the heterogeneity between studies.[17] All data were expressed as mean ± SD and statistical calculations were used to estimate means ± SD in studies which reported means ± S.E.M., median (range) and median (Q25-Q75) instead of means ± SD. Subgroup analysis were done to elucidate the source of heterogeneity. Likewise, we reported the effect size in different mean age, dose of supplementation and treatment duration. In addition, any linear relationship between sample size, treatment duration and dose of supplementation was examined by meta-regression analysis. Sensitivity analysis were done in order to find out the influence of each study on overall effect size. Moreover, Begg's and Egger's tests were used to explore the small-study effect. Furthermore, funnel plots were used to show publication bias visually. *P*-value < 0.05 was considered as significant level.

### *Certainty Assessment*

The overall certainty of evidence was rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group guidelines. Accordingly the quality of evidence was classified into four categories: high, moderate, low, and very low.[18]

## Result

### *Search results and study features*

In total 1109 publications were obtained by systematic

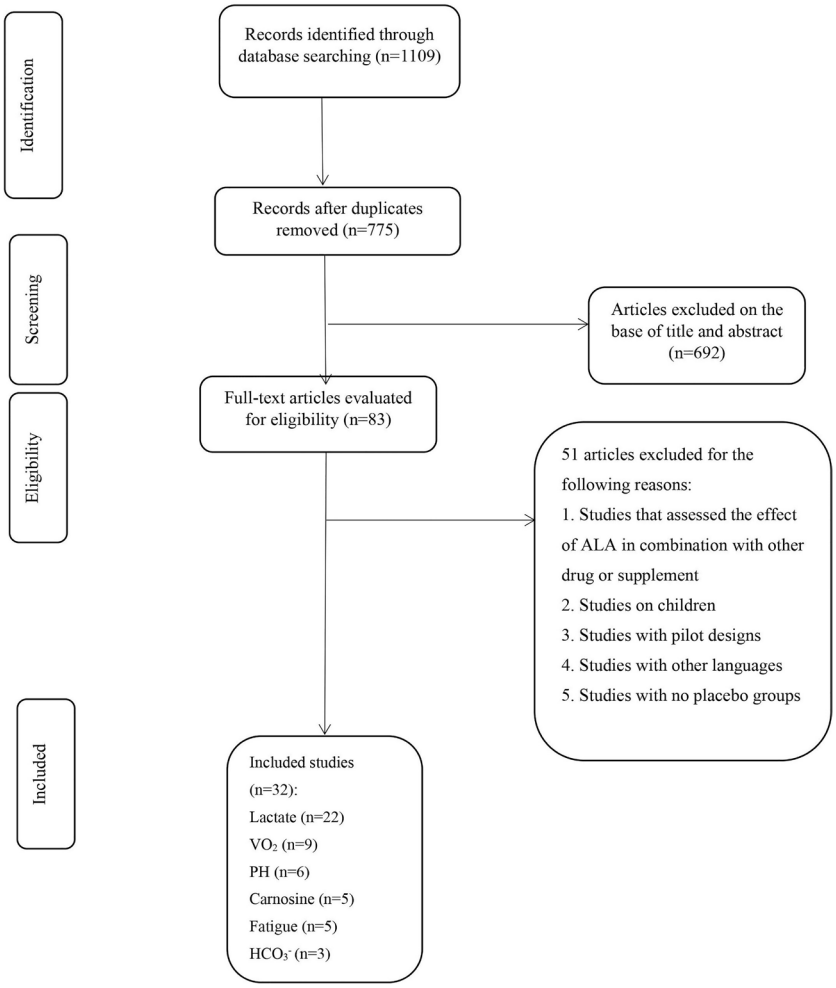



**Figure 1.** Flow diagram of study screening and selection process

search in electronic databases out of which 334 were duplicated. Afterward, title and abstract screening ended in exclusion of 692 articles and the remaining 83 articles underwent for full text evaluating. Subsequently, 51 studies did not met inclusion criteria and finally 32 studies included in the review. This process have been provided in Figure 1 according to PRISMA flow chart. Twenty two study evaluated the effect of BA on lactate,[7,9,19-36] 9 on $VO_2$,[9,21,25,30,35,37-39] 6 on pH,[7,22,26,34,36] 5 on carnosine,[30,40-43] 5 on fatigue[10,25,26,34,44] and 3 on $HCO_3^-$.[7,22,26] In total, 543 individuals aged 18 to 60 years old were included in the current study. The sample size of included studies varied from 5 to 15 in each group and were conducted from 2009 to 2019. Most of studies conducted among men. Also, most of the studies were executed in USA,[9,24,25,27,33,37,38,44] 4 in Australia,[20,26,36] 3 in Brazil,[21,22,31] 3 in England[7,19,41] one in Belgium,[34] one in Switzerland,[35] one in Korea.[29] The dose and duration of intervention varied from 4 to 10 weeks and 1.5 to 6.7 g/day respectively. General characteristics of all included studies are provided in Table 1. Quality assessment of studies was completed according to Cochrane Collaboration's risk of bias tool (Figure 2).

**Table 1.** General characteristics of included studies in the systematic review and meta-analysis.

| Journal/ first author | Year/ Country | Subjects | Sample size (IN/Cont) | Age range (year) | Duration (week) | BA dose g/day | Baseline BMI (kg/m²) IN/Cont | Male % | Main Results |
|---|---|---|---|---|---|---|---|---|---|
| Smith C.R. | 2019/ USA | Rugby players | 8 / 7 | 21.0 ± 1.8 | 6 | 6.4 | 28.65 | 100 | Lactate (NS) |
| Bassinello D. | 2018 | Physically active | 9 / 11 | 25 ± 5 | 4 | 6.4 | 26.09 | 100 | Fatigue (NS) |
| Beasley L. | 2018/ England | Physically active | 9 / 9 | 24 ± 2 | 4 | 4.8 | | 100 | Lactate (NS) |
| Bellinger P.M. | 2016/ Australia | Cyclists | 9 / 8 | 24.5 ± 6.2 | 4 | 6.4 | - | 100 | Lactate ↑ |

**Table 1.** Continued.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Brisola G.M.P. | 2018/ Brazil | Water polo players | 11 / 11 | 18±4 | 4 | 5.82 | 24.49 | 100 | Lactate (NS) |
| Donovan T. | 2012 | Amateur Boxers | 8 / 8 | 25 ± 4 | 4 | 6 | 25.96 | 100 | ↑ Lactate |
| Andrade Kratz C. | 2016/ Brazil | Judo athletes | 12 / 11 | 17±2 | 4 | 6.4 | - | 100 | Lactate ↑ pH (NS) Bicarbonate (NS) |
| Furst T. | 2018/ New York | Physically active | 7 / 6 | 60.5 ± 8.6 | 4 | 2.4 | 28.2 | - | Lactate (NS) |
| Glenn J.M. | 2015/ USA | Cyclist | 6 / 6 | 26.6 ± 1.3 | 4 | 1.6 | 22.65 | 0 | Lactate (NS) |
| Howe S.T. | 2013/ Australia | Cyclists | 8 / 8 | 24 ± 7 | 4 | 4.4 | 22.36 | 100 | Fatigue ↓ Lactate (NS) pH (NS) Bicarbonate (NS) |
| Jagim A.R. | 2013/ USA | Rugby players, Wrestlers | 10 / 11 | 20.5 ± 2.32 | 5 | 3.54 | 20.5 ± 2.32 | 100 | ↓ Lactate |
| Kern B.D. | 2011 | Football player | 7 / 8 | 18.6 ± 1.5 | 8 | 4 | 27.87 | 100 | ↓ Lactate |
| Kern B.D. | 2011 | Wrestlers | 10 / 12 | 19.9 ± 1.9 | 8 | 4 | 24.44 | 100 | ↓ Lactate |
| Kim K.J. | 2018/ Korea | Boxers | 9 / 10 | 23.0± 1.82 | 10 | 5.15 | 23.84 | 100 | Lactate (NS) |
| Kresta J.Y. | 2014 | Physically active | 8 / 7 | 21.5 ± 2.8 | 4 | 6.1 | - | 0 | Carnosine (NS) |
| Milioni F. | 2017/ Brazil | Basketball players | 12 / 10 | 17+1 | 6 | 6.4 | 22.53 | 100 | Lactate (NS) |
| Sale C. | 2011/ England | Physically active | 10 / 10 | 25 + 5 | 4 | 6.4 | 25 | 100 | ↑ Lactate |
| Sweeney K.M. | 2010/ USA | Physically active | 9 / 10 | 22.5 ± 1.7 | 5 | 5 | 30.95 | 100 | Lactate (NS) Fatigue (NS) |
| Thienen R.V. | 2009/ Belgium | Cyclists | 9 / 8 | 24.9 | 8 | 3 | - | 100 | ↑ Lactate |
| Gross M. | 2014/ Switzerland | Professional Alpine Skiers | 5 / 3 | 19.5 ± 1.1 | 5 | 4.8 | 24.38 | 100 | Lactate (NS) |
| Ducker K.J. | 2013/ Australia | Competitive team-sport athletes | 6 / 6 | 23 ± 5 | 4 | 6.6 | 25 | 100 | Lactate (NS) pH (NS) |
| Ducker K.J. | 2013/ Australia | Rowers | 7 / 9 | 26 ± 9 | 4 | 6.7 | 24.34 | 100 | Lactate (NS) pH (NS) |
| Jordan T. | 2010/ USA | Runner | 8 / 9 | 24.9 ± 5.1 | 4 | 6 | 24.45 | 100 | ↑ $VO_{2max}$ |
| Walter A.A. | 2010/ USA | Physically active | 14 / 15 | 21.5 ± 2.4 | 8 | 1.5 | 24.17 | 0 | $VO_{2max}$ (NS) |
| Wang R. | 2018 | Physically active | 11 / 8 | 22.6 ± 2.9 | 4 | 6.4 | 25.55 | 100 | $VO_{2max}$ (NS) |
| Wang R. | 2018 | Physically active | 10/ 9 | 22.5 ± 2.7 | 4 | 6.4 | 23.97 | 100 | $VO_{2max}$ (NS) |
| Varanoske A.N. | 2019 | Physically active | 12 / 8 | 22.6 ± 2.6 | 4 | 6 | 25.03 | - | Carnosine (NS) ↓ Fatigue |
| Church D. | 2017/ England | Physically active | 10 / 10 | 22.8 ± 2.7 | 4 | 6 | 24.16 | - | ↑ Carnosine |
| Carvalho V.H. | 2018 | Physically active | 14 / 14 | 36 ± 6 | 4 | 6.4 | - | 100 | ↑ Carnosine |
| Kendrick L.P. | 2009 | Physically active | 7 / 7 | 22.0 ± 2.80 | 4 | 6.4 | 20.89 | 100 | Carnosine (NS) |
| Hoffman J.R. | 2015/ USA | Physically active | 9 / 9 | 19.9 ± 0.8 | 4.28 | 6 | - | 100 | ↑ Carnosine |

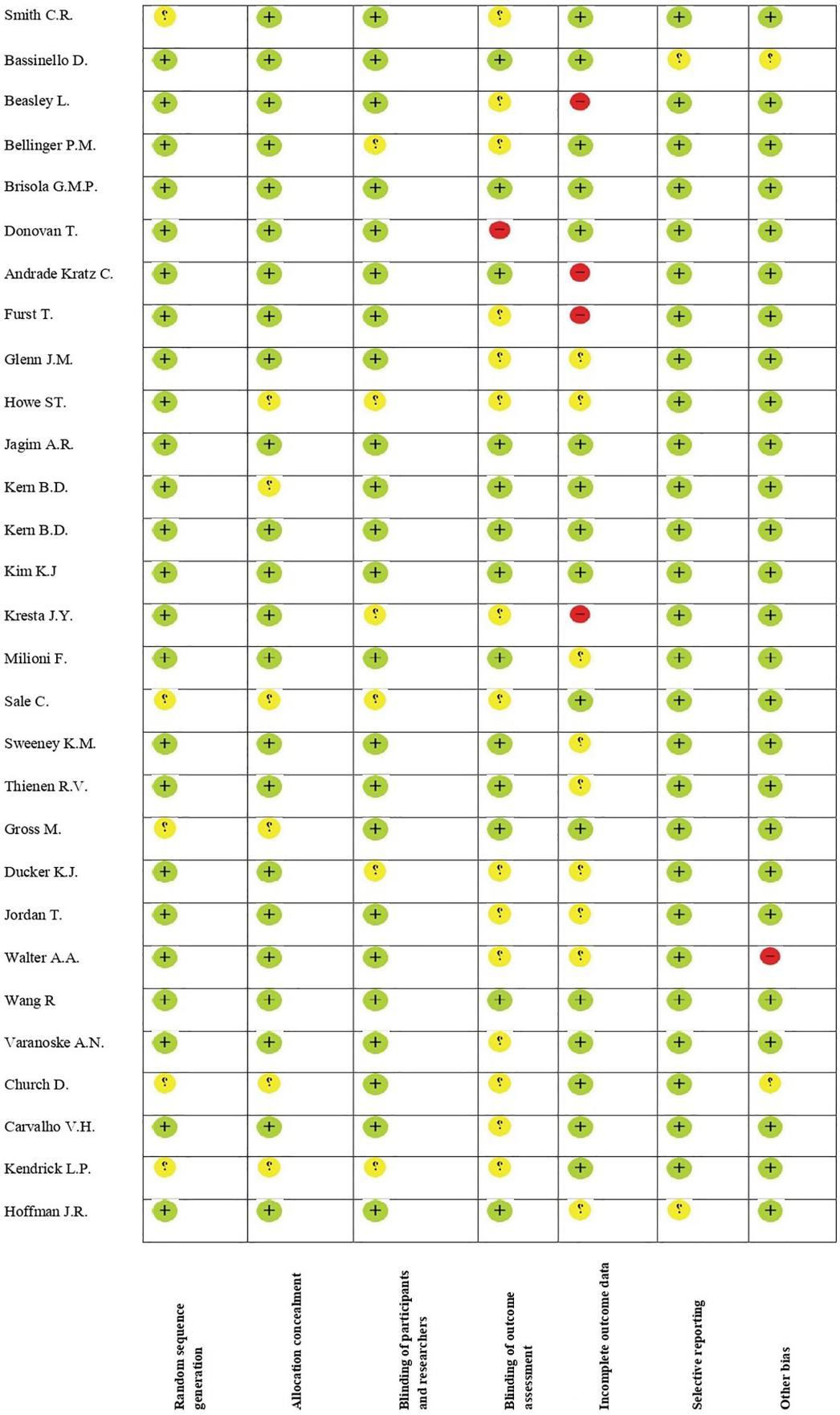



**Figure 2.** The result of risk of bias assessment using Cochrane Collaboration's risk of bias tool: each risk of bias item for included studies (green (+) means low risk of bias, yellow (?) means unclear risk of bias, red (-) means high risk of bias).

### *The effects of BA supplementation on lactate level*

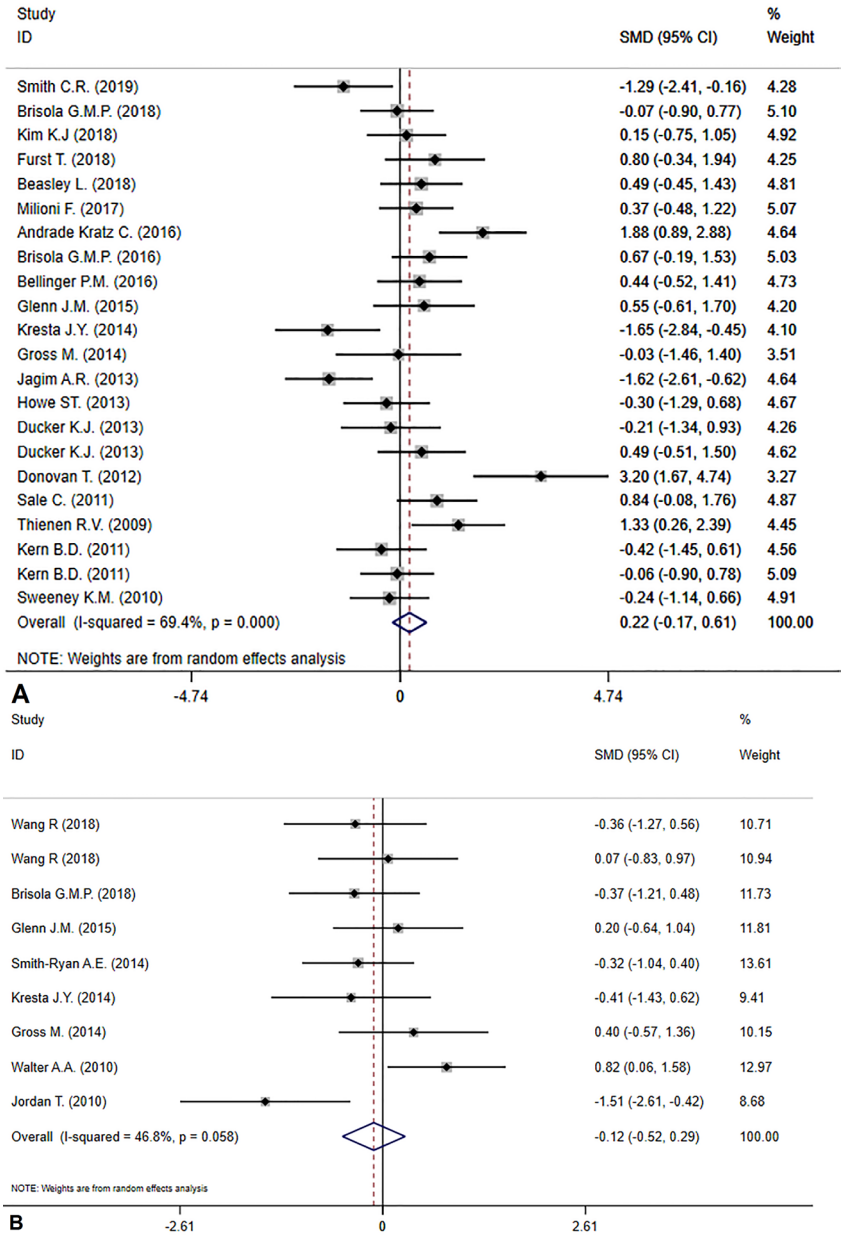
Generally, 22 studies have evaluated the effect of BA administration on lactate and the random effect model found no significant effect for BA (SMD: 0.22 mmol/L, 95% CI: -0.17, 0.61, P = 0.27) (Figure 3A). Furthermore, a high between-study heterogeneity was observed (I2 = 69.4%, p < 0.001). Subgroup analysis demonstrated marginally significant effect of duration in lower than 4 weeks (P = 0.05) (Table 2). Subgroup analysis based on mean age, sex, duration and dosage of supplementation and quality of included studies showed no significant effect of BA administration (P>0.05). Moreover, sensitivity analysis emerged no significant difference in term of removing each study. No linear relationship was observed using meta regression analysis about dose, effect size, sample size, duration and age. Egger's test showed no small study effect (P=0.632). In addition, funnel plot tried to show a symmetric distribution of studies around SMD (Figure 4).

### *The effects of BA supplementation on $VO_2$*

Totally, 9 studies have investigated the effect of BA supplementation on $VO_2$ level. BA supplementation didn't have any significant effect on $VO_2$ value (SMD: -0.12 ml/min/kg, 95% CI: -0.52, 0.29, P = 0.57) (Figure 3B) with low heterogeneity among the studies ($I^2$ = 46.8%, P = 0.058). According to subgroup analysis, treatment dosage, BMI, mean age, sex and quality of included studies have been introduced as source of heterogeneity (Table 2). BA dosage elucidated a significant decrease in $VO_2$ (P<0.05). Sensitivity analysis demonstrated no significant difference in term of removing one study.

### *The effects of BA supplementation on carnosine*

Results indicated a significant elevation in term of carnosine by BA supplementation (SMD: 1.53 mmol/kg, 95% CI: 1.08, 1.98, P <0.001) and there was no significant heterogeneity across study ($I^2$ = 10.7%, p = 0.347) (Figure 3C). Subgroup



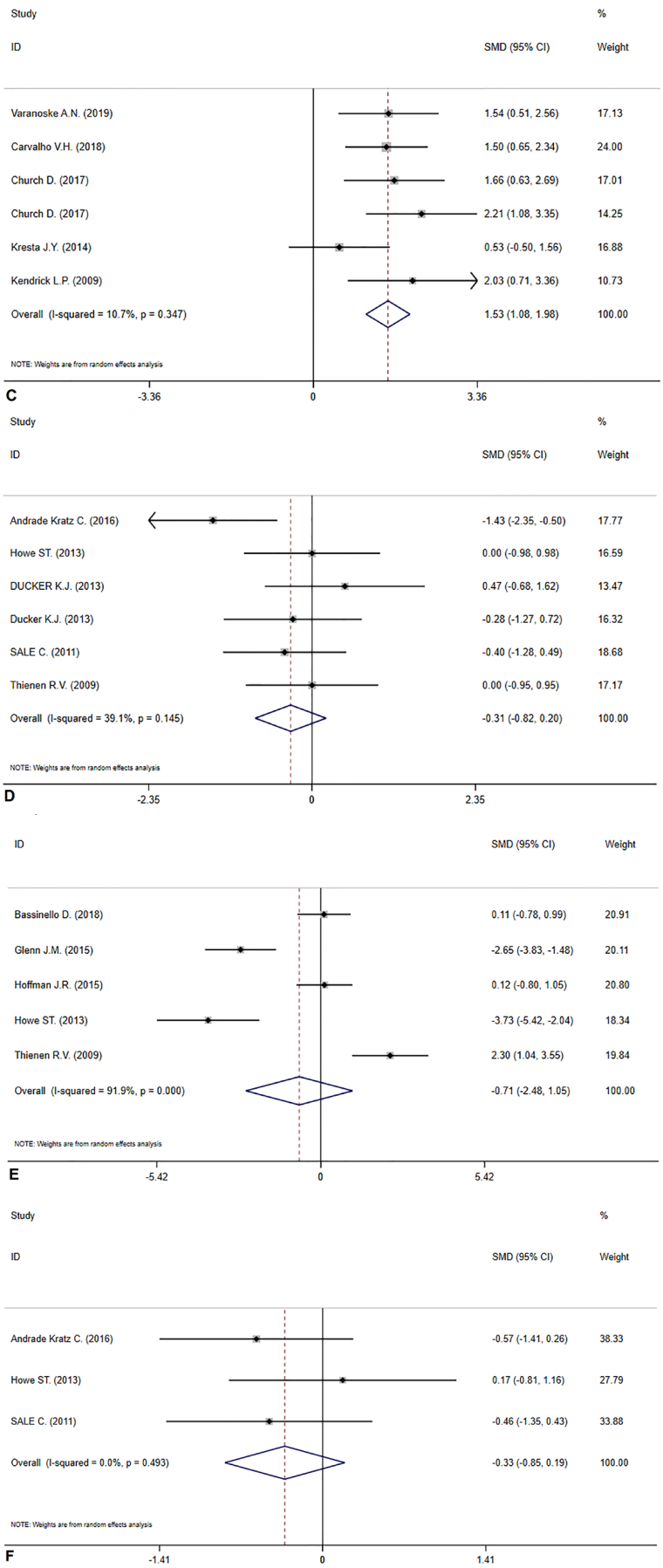



**Figure 3.** Forest plot (A, B, C, D, E, F) detailing weighted mean difference and 95% confidence intervals (CIs) of the effects of BA supplementation on lactate, $VO_{2,}$ carnosine, PH, fatigue, $HCO_3^-$ levels respectively.

**Table 2.** Pooled estimates of BA effects on recovery biomarkers within different subgroups.

| | Group | No. of comparisons | WMD or SMD (95% CI) | P-value | $I^2$ (%) | P-heterogeneity |
|---|---|---|---|---|---|---|
| Lactate | **Total** | 22 | 0.22 (-0.17, 0.61) | 0.27 | 69.4 | <0.001 |
| | **BA dosage (mg)** | | | | | |
| | >5 | 10 | 0.03 (-0.47, 0.53) | 0.91 | 57.4 | 0.01 |
| | ≥5 | 12 | 0.37 (-0.21, 0.96) | 0.21 | 75.5 | <0.001 |
| | **Intervention duration (Week)** | | | | | |
| | <4 | 13 | 0.51 (-0.00, 1.02) | 0.05 | 68.7 | <0.001 |
| | >4 | 9 | -0.19 (-0.74, 0.36) | 0.49 | 63.3 | 0.005 |
| | **Mean age (Year)** | | | | | |
| | <20 | 7 | 0.34 (-0.20, 0.89) | 0.21 | 57 | 0.03 |
| | 20 - 30 | 14 | 0.12 (-0.44, 0.68) | 0.67 | 75.2 | <0.001 |
| | >30 | 1 | 0.80 (-0.34, 1.94) | 0.17 | | |
| | **Sex** | | | | | |
| | Male | 19 | 0.26 (-0.15, 0.67) | 0.21 | 69 | <0.001 |
| | Female | 2 | -0.54 (-2.69, 1.61) | 0.62 | 85 | 0.01 |
| | Male & Female | 1 | 0.80 (-0.34, 1.94) | 0.17 | | |
| | **Quality of studies** | | | | | |
| | High | 10 | 0.06 (-0.42, 0.54) | 0.010 | 58.3 | 0.79 |
| | Moderate | 9 | 0.35 ( -0.45, 1.14) | <0.001 | 80.5 | 0.39 |
| | Low | 3 | 0.47 (-0.43, 1.38) | 0.088 | 58.9 | 0.30 |
| $VO_2$ | **Total** | 9 | -0.12 (-0.52, 0.29) | 0.57 | 46.8 | 0.05 |
| | **BA dosage (mg)** | | | | | |
| | >5 | 3 | 0.50 (0.02, 0.99) | 0.04 | 0 | 0.54 |
| | ≥5 | 6 | -0.41 (-0.78, -0.05) | 0.02 | 1.4 | 0.40 |
| | **BMI (kg/m²)** | | | | | |
| | <25 | 2 | -0.01 (-0.61, 0.58) | 0.96 | 62.5 | 0.02 |
| | >25 | 6 | -0.33 (-0.90, 0.24) | 0.25 | 0 | 0.94 |
| | NR | 1 | -0.41 (-1.43, 0.62) | 0.43 | | |
| | **Mean age (Year)** | | | | | |
| | <30 | 6 | -0.22 (-0.79, 0.35) | 0.44 | 61.8 | 0.02 |
| | >30 | 2 | 0.28 (-0.35, 0.92) | 0.38 | 0.0 | 0.76 |
| | NR | 1 | -0.41 (-1.43, 0.62) | 0.43 | | |
| | **Sex** | | | | | |
| | Male | 5 | -0.32 (-0.89, 0.25) | 0.27 | 46 | 0.11 |
| | Female | 3 | 0.27 (-0.41, 0.95) | 0.43 | 45.7 | 0.15 |
| | Male & Female | 1 | -0.32 (-1.04, 0.40) | 0.38 | | |
| | **Quality of studies** | | | | | |
| | High | 7 | -0.32 (-0.68, 0.04) | 0.341 | 11.6 | 0.07 |
| | Moderate | 2 | 0.66 (0.06, 1.26) | 0.497 | 0.0 | 0.03 |
| Carnosine | **Total** | 6 | 1.53 (1.08, 1.98) | <0.001 | 10.7 | 0.34 |
| | **Sex** | | | | | |
| | Male | 2 | 1.65 (0.94, 2.36) | <0.001 | 0.0 | 0.50 |
| | Female | 1 | 0.53 (-0.50, 1.56) | 0.31 | | |
| | Male & Female | 3 | 1.78 (1.16, 2.39) | <0.001 | 0.0 | 0.65 |

**Table 2.** Continued.

| | | | | | | |
|---|---|---|---|---|---|---|
| | **Total** | 6 | -0.31 (-0.82, 0.20) | 0.23 | 39.1 | 0.14 |
| | **BA dosage (mg)** | | | | | |
| | >5 | 2 | -0.45 (-1.19, 0.29) | 0.23 | 56.2 | 0.07 |
| | ≥5 | 4 | 0.00 (-0.68, 0.68) | 1.00 | 0.00 | 1.00 |
| **pH** | | | | | | |
| | **Quality of studies** | | | | | |
| | High | 1 | -0.40 (-1.28, 0.49) | | | 0.38 |
| | Moderate | 3 | -0.45 (-1.53, 0.63) | 0.034 | 70.5 | 0.41 |
| | Low | 2 | 0.00 (-0.68, 0.68) | 1.0 | 0.0 | 1.00 |
| | **Total** | 5 | -0.71 (-2.48, 1.05) | 0.42 | 91.9 | <0.001 |
| | **BA dosage (mg)** | | | | | |
| | >5 | 2 | 0.11 (-0.78, 0.99) | 0.47 | 0.0 | 0.98 |
| | ≥5 | 3 | -1.34 (-5.01, 2.33) | 0.73 | 95.5 | <0.001 |
| | **Intervention duration (Week)** | | | | | |
| | <4 | 4 | -1.44 (-3.16, 0.28) | 0.10 | 89.6 | <0.001 |
| **Fatigue** | ≥8 | 1 | 2.30 (1.04, 3.55) | <0.001 | | |
| | **Mean age (Year)** | | | | | |
| | 30≥ | 4 | -0.21 (-2.03, 1.61) | 0.81 | 90.4 | <0.001 |
| | >30 | 1 | -2.65 (-3.83, -1.48) | <0.001 | | |
| | **Quality of studies** | | | | | |
| | High | 3 | -0.77 (-2.40, 0.87) | <0.001 | 87.9 | 0.35 |
| | Low | 2 | -0.69 (-6.59, 5.22) | <0.001 | 96.8 | 0.81 |

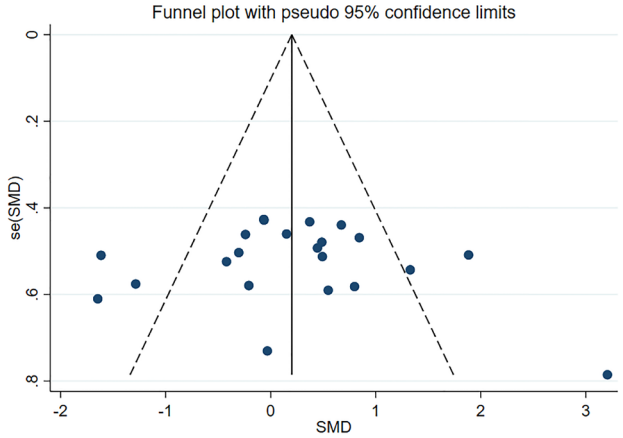



**Figure 4.** Funnel plot displaying publication bias in the studies reporting the effects of BA supplementation on lactate level.

analysis recognized sex as a source of heterogeneity (Table 2). Male and the group containing both genders revealed significant effect on carnosine (SMD: 1.65 mmol/kg, 95% CI: 0.94, 2.36, P <0.001) and (SMD: 1.78 mmol/kg, 95% CI: 1.16, 2.39, P <0.001) respectively. Sensitivity analysis showed no significant difference about removing one study.

### *The effects of BA supplementation on pH*

The results of present meta-analysis have demonstrated that BA administration have no significant effect on pH level (SMD: -0.31, 95% CI: -0.82, 0.20, P = 0.23) and no significant heterogeneity was detected between studies (I2 = 39.1%, p = 0.145) (Figure 3D). Intervention dosage has been considered as a source of heterogeneity based on subgroup analysis (Table 2). BA supplementation showed a significant effect on pH in >5 mg/day (SMD: 0.00, 95% CI: -0.68, 0.68, P >0.05). No significant difference was reported by removing one single study in sensitivity analysis.

### *The effects of BA supplementation on fatigue*

The effect of BA on amending fatigue was not statistically significant (SMD: -0.71, 95% CI: -2.48, 1.05, P = 0.42) (Figure 3E). However, the amount of heterogeneity was high between studies ($I^2$ = 91.9%, p < 0.001) and treatment dosage was recognized as sources of it (Table 2). Except a significant effect of >5 mg/day dosage subgroup on fatigue value (SMD: 0.11, 95% CI: -0.78, 0.99, P = 0.47), there were no significant effects of BA on fatigue level after subgroup analysis by intervention dosage, duration, mean age of participants and quality of included studies. Moreover, there was no significant single study effect using sensitivity analysis. Begg's tests were performed to show small-study effects and no significant effect was reported (P=0.446).

### *The results of the meta-analysis of the effects of BA supplementation on $HCO_3^-$*

BA administration could reduce $HCO_3^-$ level but has not a significant impact on $HCO_3^-$ (SMD: -0.33, 95% CI: -0.85, 0.19, P = 0.21) and there was no significant between-study heterogeneity ($I^2$ = 0.0%, P = 0.49) (Figure 3F). Sensitivity analysis demonstrated that removing single study makes no significant difference. Also, no significant small-study effect was shown through performing Begg's tests (P= 0.155).

### *Grading of evidence*

To assess the quality of evidence for outcomes, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework was performed. The evidence about VO2 and $HCO3^-$ were downgraded to moderate. According to the GRADE protocol, evidence regarding lactate, carnosine, pH and fatigue was identified as very low quality (Supplementary data, Table S1).

## Discussion

The current systematic review and meta-analysis of 32 RCTs was performed to assess the effects of BA supplementation on recovery biomarkers in physically active adults. Our results revealed a significant increase of carnosine level in term of BA supplementation compared to placebo group. Several studies concluded that increase in physical performance after BA supplementation may lead to an increase in muscular carnosine concentrations.[45-47] Likewise, buffering effect of carnosine which regulate intracellular pH, an increase in Calcium ($Ca^{2+}$) sensitivity in muscle fibers, and an increase in $Ca^{2+}/H^+$ ion exchange contribute to an enhancement in muscular contractility that are associated with increasing level of carnosine.[3] Previous studies had demonstrated that carnosine, the main buffering substance of the intramuscular $H^+$, was increased following BA supplementation and prevented the decline of intracellular pH in high-intensity exercise.[48,49] In this regard, our findings illustrated the effects of BA supplementation on increasing carnosine level with no significant changes in blood $HCO_3^-$ and pH levels. However, no significant effects was shown for blood lactate, $HCO_3^-$, and pH level following BA supplementation. Similarly, no significant changes was shown about $VO_2$ value and fatigue in comparison with placebo group. Elevated blood lactate levels contribute to glycolytic metabolism. Hence, the produced and accumulated hydrogen cations during athletic activities induce muscle acidosis.[50] Thereby, keeping intracellular pH may favor the delay of fatigue additionally to overall physical performance during exercise. The intense and acidotic nature of sport activities and following fall in blood pH, it was hypothesized that athletic performance could benefit from BA supplementation. It seems that the types of exercise to induce the anaerobic glycolytic metabolism and accumulation of $H^+$ could be contributing to the inconsistency in studies outcomes. Therefore, high-intensity and short-term exercises are more susceptible to be improved by buffering agents. In this regard, a meta-analysis reported that BA supplementation could greatly improve short term exercise lasting for a 1–4 min compared to long term exercises.[11] Patel *et al.*[51] indicated that accumulation of blood lactate contributed to a significant trial × time interaction post-supplementation which was not significantly different between study groups. They reported that high-intensity cycling capacity did not increase in normoxia by BA supplementation; also BA did not improve cycling capacity in hypoxia despite reduced exercise capacity under hypoxic conditions.Contrarily, the positive effects of BA supplementation in sports such as cycling, boxing, soccer, swimming, and running have been reported by other studies.[23,34,53-56] It seems that blood pH and lactate concentration are not more sensitive to measures or detect any small changes in intramyocellular levels.[52] Our findings are in line with previous observations, as several studies have generally failed to report any significant positive effects of BA supplementation on athletic recovery-related parameters.[26,57,58] Until now, the exercise-induced changes in muscle pH have been outlined from changes in venous blood pH, but the interstitial pH and blood pH correlation cannot be easily predicted because the venous blood is mixed with blood-draining inactive tissue. Therefore, blood pH value could not reflect pH changes at the intramuscular level.[59]

To the best of knowledge, this is the first meta-analysis evaluated the effect of BA supplementation on exercise recovery variables including fatigue, blood levels of lactate, $HCO_3^-$, pH, carnosine, and $VO_2$ value. Also, the meta-analysis was performed based on subgroups to additional identify the results of each relevant factor. Moreover, publication bias was checked for all of the assessed related factors. Our study might have some limitations that could influence the obtained results; therefore, these limitations should be considered in the interpretation of the results. First, the study population of included studies had different types of exercise and physical activity levels. Second, the included studies had small sample sizes. However, this meta-analysis was sufficiently powered to detect the significant effect of the intervention. Third, the adjusted confounding factors were different among the included studies. However, the effects of some confounding factors, such as dietary intakes, were not considered in most of the studies. Forth, we have not registered the protocol of the present study in the PROSPERO which may cause some aspects of bias. Finally, as a common limitation of meta-analysis studies we can mention the possibility of unpublished trials with negative results which cannot be ruled out. Whereas, as a strength of the current study, subgroup analysis was done and detected the heterogeneity of eligible studies and this heterogeneity might be attributed to differences in study design, the baseline characteristics and number of participants, and supplement dosage.

## Conclusion

In conclusion, this meta-analysis of RCTs showed that BA supplementation exhibits a statistically significant effect on enhancing carnosine concentration. It may underlie the ergogenic effects of BA supplementation and highlight the evidence-based potential usage of BA as an ergogenic nutritional supplement in physically active individuals. However, the results of this study indicated that BA administration had no significant effect on fatigue delay and blood levels of lactate, $HCO_3^-$, pH, and $VO_2$ value. According to high heterogeneity that has been observed for some outcome variables, further prospective studies with a correct methodology and high quality should

be conducted to clarify how this supplement should be introduced in clinical practice.

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## Author Contributions
Mahsa Mahmoudinezhad: Investigation, Writing - Original Draft. Meysam Zarezadeh: Methodology, Formal Analysis. Fatemeh Pourteymour Fard Tabrizi: Formal Analysis, Parsa Jamilian: Writing - Review & Editing, Parmida Jamilian: Writing - Review & Editing, Alireza Ostadrahimi: Writing - Review & Editing

## Conflict of Interest
The authors report no conflicts of interest.

## Supplementary Data
Supplementary data, Table S1, are available at https://doi.org/10.34172/PS.2022.40.

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