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Original Article

Fruit-derived Polyphenol supplementation improves exercise performance: a meta-analysis of 29 randomised controlled trials

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Abstract:
Fruit-derived polyphenols (FDP) are rich in antioxidants and have anti-inflammatory properties. They have also been shown to improve exercise performance. FDP supplementation may increase muscle oxygenation during exercise through the nitric oxide (NO) pathway by increasing both NO bioavailability and endothelial NO synthase expression. The current meta-analysis systematically evaluates the relevant randomised controlled trials to verify whether FDP supplementation improves exercise performance compared to the placebo (PLA). Relevant studies have been examined using five electronic databases: PubMed, EMBASE, Ovid [MEDLINE], SPORTDiscus and Web of Science. Other relevant articles from grey literature sources were also manually examined. Fifty-five trials from 29 studies met the inclusion criteria, involving a total of 651 subjects. The overall effect size yielded an average standardised mean difference (SMD) of 0.29 (95% CI: 0.21 to 0.38, p<0.001), indicating that FDP supplementation provides a small yet significant performance benefit over PLA. In the subgroup analysis, the current study found that the highest effect size is from the co-ingestion of multiple sources of FDP (SMD = 0.40 [95% CI: 0.13 to 0.65], p<0.001), followed by cherries and berries, then pomegranates (SMD = 0.28 [95% CI: 0.18 to 0.37], p<0.001 and SMD = 0.23 [95% CI: 0.02 to 0.43], p=0.03, respectively). These findings suggest that the ergogenic effects of dietary polyphenol supplementation naturally sourced from fruit does improve exercise performance and can potentially benefit athletes in the context of supplementation strategy.
Key Words*:* - **Polyphenol, Fruit, Exercise, Exercise performance, Supplementation**

Introduction

Fruit-based foods naturally contain polyphenols that have a wide range of complex structures. Polyphenols can be categorised into many classes depending on the strength of the phenolic ring, although the main ones are phenolic acids, flavonoids, phenolic alcohols and lignans (Durazzo et al., 2019). Polyphenols are a group of biologically active compounds in fruit and plant-based foods (Tosif et al., 2021). They are described as secondary metabolites and are involved in a wide range of critical processes within fruit and plants, including growth, pigmentation, pollination and resistance to pathogens and environmental stressors (Anjorin et al., 2022). The total daily dietary intake of polyphenols can be as high as 1 g·day^{-1}, which is 10 to 100 times higher than the intake of other 'phytochemicals' of well-known antioxidants such as vitamin C, vitamin E and carotenoids (Draeger et al., 2014). Structurally, polyphenols are characterised by two or more hydroxyl groups attached to one or more benzene rings (Liu et al., 2020). There are over 8000 polyphenols currently identified. According to the range and variation of in vivo effects, polyphenols have been distinguished and categorised into four main groups: flavonoids, stilbenes, lignans and phenolic acids (Ebrahimi & Lante, 2021).

Polyphenol supplementation is currently controversial due to recent evidence that antioxidant-rich supplementation may inhibit exercise training adaptations (Kay et al., 2017). It is a widely held belief that polyphenols, a known source of antioxidants, may have different mechanisms to enhance athletic performance. This assumption is supported by the emerging evidence indicating that chronic polyphenol supplementation promotes mitochondrial biogenesis in skeletal muscle (Chodari et al., 2021a). The evidence specifically suggests that polyphenol supplementation may induce stress-related cell signalling pathways that enhance the expression of genes-encoding cytoprotective proteins, such as nuclear factor erythroid-2-related factor 2 (NRF2), which ultimately improves redox balance (Ge et al., 2019; Jumat et al., 2021). Certain polyphenols (such as quercetin, resveratrol and curcumin) can also modulate muscle function and mitochondrial biogenesis by activating the protein-coding gene sirtuin 1 (SIRT1) and increasing the activity of peroxisome proliferator-activated receptor-c coactivator (PGC-1a) (Hejazi et al., 2020). A more recent finding suggests that polyphenol supplementation may

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increase the phosphorylation of endothelial nitric oxide synthesis, enhancing the flow-mediated dilatation and endothelial function in humans (Jumat et al., 2021; Stromsnes et al., 2020).

In recent years, the popularity of consuming naturally occurring plant extracts and phytochemicals to enhance physical performance, exercise recovery and health has skyrocketed at both the academic and Olympic levels, with vitamins and multivitamins being the most popular options (Piattoly, 2022). Sport supplements are also becoming increasingly popular (Linoby, Azrin, et al., 2020). As athletes push the limits of what is physically possible, the difference between winning and losing comes down to a matter of millimetres and milliseconds. Polyphenol supplementation may well impose ergogenic effects on the rate of blood flow and maximum cardiac output during high-performance activities, which are important determinants of cardiovascular performance. A previous study claimed that polyphenol intake may enhance performance to a relatively similar degree as synthetically derived supplementation, such as caffeine (Gómez-Mejía et al., 2022).

Among athletes, using supplementation with non-traditional and biological compounds has become widespread. Despite the increasing research, evidence remains insufficient to either recommend or condemn the use of polyphenol supplementation (whether it is certain types or specific doses) for recreational, competitive or elite athletes. Although fruit-derived polyphenol supplements do contain antioxidant properties, they are currently controversial since they may inhibit training adaptations (Bowtell & Kelly, 2019).

Several meta-analyses that explore the ergogenic impact of polyphenols have been published, yielding varying degrees of performance outcomes (Bowtell & Kelly, 2019; Haghighatdoost et al., 2020; Lamport & Williams, 2021; Morton & Braakhuis, 2021). However, to date, no published systematic meta-analysis is available to specifically examine various polyphenols sourced from fruit as well as their impact on exercise performance. In this study, we systematically evaluate the relevant randomised controlled trials using the meta-analytical approach to determine whether FDP supplementation does improve exercise performance as compared to the placebo (PLA). This meta-analysis further investigates various potential sources to contribute to the current knowledge. Subgroups were analysed in terms of the type of exercise (aerobic vs. anaerobic), supplementation protocol (acute vs. chronic) and source of polyphenols (cherries and berries vs. pomegranates vs. cocoa vs. mixed FDP).

Material & methods

Search Strategy and Study Selection

Five different electronic databases were thoroughly searched: PubMed, EMBASE, Ovid [MEDLINE], SPORTDiscus and Web of Science. The final search date was on April 1, 2022. Other eligible studies from several different sources were manually examined (Microsoft Academic Search, base-search.net, jurn.org, Search Oxford Libraries Online and ProQuest Global). The following combination of keywords were used during the search: ‘polyphenol’, ‘polyphenols’, ‘flavonoid’, ‘flavonoids’, ‘tannis’, ‘lignans’, ‘stilbenes’, ‘curcumin’, ‘phenolic acids’, ‘aerobic’, ‘anaerobic, ‘exercise’, ‘physical exercise’, ‘physical activity’, ‘exercise training’ and ‘exercise performance’. All research included in the meta-analysis had met the following eligibility criteria: (1) employed healthy adult human subjects; (2) implemented a randomised controlled trial study design with a control group (CON) or placebo (PLA); (3) administered polyphenol supplementation from fruit-sources before and/or during the exercise trial; (4) used direct measures and quantifiable effect size from exercise performance data; (5) published in the English language; and (6) no co-ingestion was present with other potential ergogenic aids (Linoby, Md Yusof, et al., 2020). Following the removal of duplicates from the initial searches, the remaining records were screened on the basis of title and abstract. All studies deemed potentially relevant proceeded to a full-text screening. Four investigators (F.N.S.Z., A.L., S.M. & N.M.) independently conducted the screening process to ensure consistency and reduce bias throughout all screening stages (title, abstract and full-text screening). In case of any disagreements regarding the screened records, the investigators would discuss with other team members until a consensus is reached and the matter is resolved. A final record of 55 trials from 29 manuscripts met the above-mentioned eligibility criteria. The search strategy and study selection process adhered to the latest guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Stewart et al., 2015).

Data Extraction and Quality Assessment

Specific relevant variables from the eligible studies were systematically assigned to a coding sheet. The authors were contacted when necessary to obtain key information on statistical variables (p-value, mean, standard deviations, etc.). A number of variables were extracted from each trial, including (1) participant’s characteristics; (2) study design; (3) intervention characteristics, such as treatment duration and timing of treatment; (4) exercise testing characteristics, such as testing protocol and type of exercise testing; and (5) specific outcome of each trial.

Three independent investigators (F.N.S.Z., A.L. & I.N.) evaluated the risk of bias for all eligible studies using the risk of bias tool by Cochrane Collaborations (Higgins et al., 2011). The selected bias domains that were analysed included the randomisation of allocation sequence, allocation concealment, blinding bias and selective outcome reporting. These sources of bias were classified as either high, low or unclear risk of bias. Classification was based on the information presented in each eligible study.

Statistical Analysis

An estimate of the mean summary weighted effect was conducted using a random-effects model. Standard errors were calculated using the p-value (Giles, 2004). If the exact p-value was not reported in the research, the corresponding author would then be contacted. If this information could not be obtained, estimated p-values are then calculated using the methods presented by Altman & Bland (2011). A subgroup analysis was also accomplished to compare the energy system (trained vs. untrained), supplementation protocol (acute dosage vs. chronic dosage) and types of polyphenol (cherries and berries vs. cocoa vs. pomegranates vs. mixed FDP; PP others).

The funnel plots and Egger's test were employed to examine publication bias. The trim-and-fill examination was used to adjust any identified publication bias. The heterogeneity of treatment effects from the included research was statistically evaluated using a Q-test (presence of variation between pooled effect size) and I^2 statistic (degree of heterogeneity). The benchmarks for the I^2 value were interpreted according to the guidelines outlined by Harris et al. (2008). Overall effect size summary with the corresponding 95% confidence intervals (CI) were calculated, with significant results that did not include zero. The standardised mean difference (SMD) and its 95% confidence intervals were calculated using the Comprehensive Meta Analysis (CMA; version 3.3.070, Biostat Inc, New Jersey, USA). A forest plot was used to determine data patterns.

Results

Our database search results identified 2642 relevant articles. After removing duplicate titles, we were left with 361 articles. Following a full-text assessment of the eligibility criteria outlined earlier, we identified 29 publications describing 55 different trials that fit our criteria for inclusion in the meta-analysis.

Meta-Analyses

As shown in Figure 1, FDP interventions have led to statistically significant improvements in exercise performance as compared to PLA. The results of the pooled standardised mean difference (SMD) estimates of the included research indicate that exercise performance does improve with FDP supplementation as compared to the PLA group (overall SMD = 0.29 [95% CI: 0.21 to 0.38], $p<0.001$).

Subgroup Analysis

A subgroup was formed on the type of performance test used (aerobic vs. anaerobic). The subgroup analysis revealed that the effect size of aerobic exercise (SMD = 0.34 [95% CI: 0.22 to 0.46], $p<0.001$) is slightly larger than anaerobic exercise (SMD = 0.29 [95% CI: 0.12 to 0.36], $p<0.001$). A subgroup comparison of the supplementation protocol (i.e., acute dosage vs. chronic dosage) was further conducted. The subgroup analysis shows that the effect size of acute dosage (SMD = 0.30 [95% CI: 0.18 to 0.42], $p<0.01$) is relatively similar in comparison to chronic dosage (SMD = 0.29 [95% CI: 0.17 to 0.41], $p<0.001$). A subgroup comparison of the source of polyphenol was also performed. Mixed FDP (denoted as 'PP others') yielded the highest and statistically significant effect size (SMD = 0.40 [95% CI: 0.13 to 0.65], $p<0.001$). This was followed by different polyphenol groups: cherries and berries (SMD = 0.28 [95% CI: 0.18 to 0.37], $p<0.001$) and pomegranates (SMD = 0.23 [95% CI: 0.02 to 0.43], $p=0.03$). In contrast, an insignificant change in exercise performance outcome was evident in the subgroup analysis of cocoa-based polyphenols (SMD = 0.38 [95% CI: -0.31 to 1.07], $p=0.28$).

Publication Bias

The funnel plot of the main analysis revealed a small to moderate asymmetry to the left, indicating a possible publication bias or a systematic difference between studies of higher and lower precision, as supported by the results of Egger's regression intercept ($\beta = 1.74$ [95% CI: 0.76 to 2.73], $p<0.01$). Heterogeneity analysis was conducted to determine the homogeneity status with regard to the exercise performance outcome. A significant (small to moderate) heterogeneity was evident in all included trials ($p<0.05$; $I^2 = 32.2\%$). However, the source of heterogeneity in each of these two subgroups may be due to the related variables, as shown in the subgroup analysis presented in the current study (e.g., type of energy system used in the exercise performance test, supplementation protocol and source/type of polyphenol supplementation).

Study Quality

Overall, no high risk of bias was found after analysing the potential sources of bias. Since the random sequence generation and allocation concealment were not specifically reported in all included studies, they were regarded as unclear risk of bias. The majority of studies (~92%) had clearly stated their method of blinding participants and assessors. There was no evidence of reported bias in all included studies.

Study name	Std diff in means	Standard error	p-Value
Allen (2020)	0.418	0.324	0.197
Allgrove et al. (2011)	0.083	0.224	0.712
Brandenburg & Giles (2021)	0.010	0.302	0.973
Cases et al. (2017)	0.274	0.367	0.455
Cook et al. (2015)	0.666	0.295	0.024
Crum et al. (2017) A	0.195	0.357	0.586
Crum et al. (2017) B	0.217	0.358	0.544
de Lima Tavares Toscano et al. (2020)	0.836	0.310	0.007
Decroix et al. (2017)	0.719	0.324	0.026
Deley et al., (2017) A	0.072	0.183	0.693
Deley et al., (2017) B	0.308	0.184	0.094
Dostal et al. (2019)	0.769	0.232	0.001
Fryer et al. (2020) A	0.024	0.289	0.934
Fryer et al. (2020) B	0.297	0.295	0.313
Godwin et al. (2017) A	0.331	0.342	0.334
Godwin et al. (2017) B	0.187	0.336	0.578
Godwin et al. (2017) C	0.224	0.337	0.506
Gough et al. (2017)	1.173	0.392	0.003
Howatsen et al. (2022) A	0.609	0.394	0.122
Howatsen et al. (2022) B	0.047	0.385	0.904
Kang et al. (2012) A	0.422	0.213	0.047
Keane et al., (2018) A	0.313	0.309	0.310
Keane et al., (2018) B	0.740	0.340	0.030
Keane et al., (2018) C	0.825	0.349	0.018
Levers et al. (2015)	-0.106	0.418	0.799
Machin et al. (2014) A	0.652	0.284	0.022
Machin et al. (2014) B	0.445	0.271	0.100
Machin et al. (2014) C	0.090	0.259	0.728
Machin et al. (2014) D	0.000	0.258	1.000
McCormick et al. (2016) A	0.000	0.136	1.000
McCormick et al. (2016) B	0.148	0.137	0.279
McCormick et al. (2016) C	0.222	0.138	0.107
McCormick et al. (2016) D	-0.111	0.137	0.415
Murphy et al. (2017)	0.790	0.362	0.029
Perkins et al., (2015) A	0.723	0.311	0.020
Perkins et al., (2015) B	0.744	0.313	0.018
Perkins et al., (2015) C	0.716	0.311	0.021
Perkins et al., (2015) D	0.723	0.311	0.020
Peschek et al. (2013)	0.014	0.354	0.969
Ranchal-Sanchez et al. (2020) A	0.140	0.225	0.533
Ranchal-Sanchez et al. (2020) B	0.053	0.224	0.814
Ranchal-Sanchez et al. (2020) C	0.011	0.224	0.960
Ranchal-Sanchez et al. (2020) D	0.525	0.238	0.028
Ranchal-Sanchez et al. (2020) E	0.468	0.236	0.047
Ranchal-Sanchez et al. (2020) F	0.265	0.228	0.244
Rayane et al. (2020)	0.048	0.267	0.857
Toscano et al. (2015)	0.464	0.384	0.227
Trexler et al. (2014) A	0.672	0.254	0.008
Trexler et al. (2014) B	0.552	0.246	0.025
Trexler et al. (2014) C	-0.403	0.239	0.091
Trinity et al. (2014)	-0.487	0.305	0.111
Trombold et al. (2011) A	0.470	0.256	0.066
Trombold et al. (2011) B	0.129	0.244	0.596
Willems et al. (2016) A	0.328	0.285	0.249
Willems et al. (2016) B	0.405	0.289	0.160
	0.293	0.043	0.000

Statistics for each study

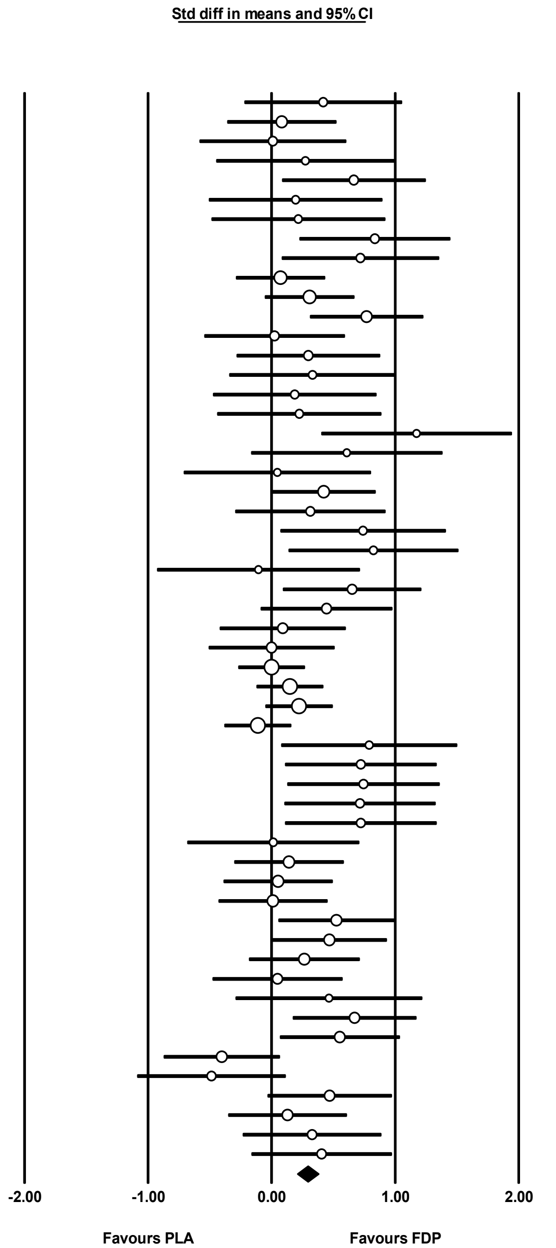

Fig. 1. Forest plot and overall effect size estimates for the outcome of fruit-derived polyphenol supplementation on exercise performance

Discussion

The findings from the current study are in agreement with previous review papers that described how FDP supplementation may have ergogenic effects which can effectively reduce the development of fatigue (Bowtell & Kelly, 2019). However, these general reviews did not specifically nor systematically evaluate the ergogenic effect of FDP, and how such effects may influence the type of exercise and energy system, supplementation protocol and types of polyphenol. The current study clarifies the possible ergogenic potential of FDP supplementation on exercise performance. This meta-analysis compared between the type of exercise (aerobic *vs*. anaerobic), supplementation protocol (acute vs. chronic) and types of polyphenol (cherries and berries *vs*. pomegranate *vs*. cocoa *vs*. mixed polyphenol) with FDP administration to further clarify the potential fitness dependency of FDP's ergogenic effects. Overall, this meta-analysis suggests that FDP supplementation can significantly improve exercise performance. This enhancement increases with the co-ingestion of mixed FDP, cherries & berries as well as pomegranates, regardless of supplementation protocol and energy system.

This meta-analysis found a statistically significant small treatment effect on exercise performance (SMD = 0.293) in favour of FDP compared to PLA conditions. A previous review paper suggested that FDP supplementation is associated with a small to moderate improvement in exercise performance. The improvement in exercise capacity from polyphenol-based supplementations may be related to nitric oxide (NO) synthesis, which can help match the tissue perfusion of both oxygen and other substrates to working muscles during exercise (Linoby et al., 2020). Among its many signalling abilities, it is well known that NO is crucial for skeletal muscle glucose absorption and fat oxidation (Asraff et al., 2022). Thus, it is probable that during an activity test, skeletal muscle glucose absorption does significantly increase with the rise in NO production after FDP administration. If so, it is likely that increased FDP consumption and decreased use of muscle glycogen have contributed to exercise performance enhancements (Linoby et al., 2020).

The current meta-analysis provides up-to-date data regarding the effect of FDP supplementation on the type of exercise performance (aerobic vs. anaerobic). The subgroup analyses confirmed that FDP interventions have a greater effect size on aerobic exercise compared to anaerobic exercise. In an experimental analysis, the sprint performance of 13 healthy males was examined using a motorised treadmill. It was revealed that 300 mg of blackcurrant ingested for 7 days increased the sprint performance by ~9%, with a substantially greater total distance covered (~11%) during the intermittent running protocol (Perkins et al., 2015). Greater improvement in aerobic compared to anaerobic endurance is expected considering the involvement of NO, which enhances oxygen delivery and tissue oxygenation, especially during mismatched oxygen demand-and-supply during exercise. The study outcomes of the subgroup analysis indicate that supplementation protocol (i.e., acute vs. chronic) has a negligible effect on the ergogenic potential of FDP administration. The difference in effect size between acute and chronic supplementation of FDP was merely 2%, with acute supplementation producing a higher effect size compared to chronic ingestion. Several studies suggested that chronic vitamin-based antioxidant supplementation may have a detrimental effect on performance. In two consecutive research, the harmful effect of antioxidant ubiquinone-10 supplementation on human performance was proven after a high-intensity training program. This may indirectly explain the lower magnitude of effect size with chronic FDP supplementation compared to acute ingestion (Cooke et al., 2008). Consuming FDP in acute dosages may inhibit superoxide-producing enzymes such as NADPH oxidase, thereby enhancing antioxidant enzyme and vascular activity rather than in chronic supplementation (Sylvester et al., 2022).

The most significant outcome of the current study is that the source of FDP considerably influences its ergogenic capacity. The trials that examined the effects of consuming different mixtures of FDP yielded the highest effect size (by 0.40), followed by cherries and berries (by 0.28) and pomegranates (by 0.23). Cases et al. (2017) found that the effects of grape and pomegranate mixtures led to a significant increase in total power output, maximal peak power output and average power developed during high-intensity exercise. Cherries and berries are nutritious fruit rich in anthocyanins, a subclass of dietary polyphenols that play an important role in both defensive and physiological functions (Trombold et al., 2011). A study by Keane et al. (2018) revealed that peak power output and total work done during a 60-s sprint increased by 9.5% and 10%, respectively, after using the Montmorency tart cherry supplementation. Despite the relatively large effect size, an insignificant change in the outcome of exercise performance was evident in the subgroup analysis of cocoa-based polyphenols (SMD = 0.38, $p = 0.28$). Eligible research on cocoa supplementation are limited with only 2 trials included in the current analysis. Future research should therefore focus on cocoa supplementation to explore its ergogenic potential.

Several limitations exist in the present study. Publication bias must be taken seriously since it can easily exaggerate the effect or even simulate therapeutic effects where none exists. It is impossible to rule out the possibility of publication bias due to the shape of the funnel plot. A seemingly plausible explanation for the asymmetry is inconsistency in the exercise intervention procedure, supplementation protocol, subject's training status and source of FDP.

Conclusions

The outcomes of the meta-analysis indicate that fruit-derived polyphenol supplementation is likely to significantly improve exercise performance as compared to the placebo. The overall effect size yielded an average standardised mean difference of 0.29, indicating that fruit-derived polyphenol supplementation provides a small yet significant performance benefit over the placebo. In the subgroup analysis, the highest effect size was found with the co-ingestion of multiple sources of fruit-derived polyphenols, followed by cherries and berries, then pomegranates. However, our analyses also suggest that this advantage is contingent on the source of FDP administered, supplementation protocol and type of predominant energy system used in the exercise tests. Currently, only a small number of studies have examined the ergogenic effects of FDP. The lack of adequate replication of certain variables prevents the generalisation of the meta-analysis results performed in this study. To determine the experimental conditions on whether FDP is more or less likely to be ergogenic, further investigations on the effects of FDP supplementation and exercise testing protocols are required. However, preliminary evidence suggests that FDP supplementation may improve exercise performance, thereby supporting the use of this natural fruit-sourced supplement.

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