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Review Article

Multi-Target Cardioprotective Agents: Molecular Docking, Pharmacological Evaluation, and Translational Perspectives (2020–2025)

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ABSTRACT

Cardiovascular diseases (CVDs) remain the leading cause of global mortality, while most current therapies target only specific disease pathways. Withania somnifera (Ashwagandha), a medicinal plant widely used in traditional medicine, contains bioactive steroidal lactones known as withanolides with significant pharmacological activities. This review summarizes studies published from 2020–2025 on the molecular docking, pharmacological evaluation, and ADMET profiling of major withanolides, including withaferin A and withanolide D, as potential multi-target cardioprotective agents. The review discusses the phytochemistry and classification of withanolides along with their antioxidant, anti-inflammatory, lipid-modulating, endothelial-protective, and stress-regulating mechanisms. Additionally, molecular docking studies against major cardiovascular targets such as ACE, eNOS, TNF-α, and COX-2 are critically analyzed and correlated with available in vitro and in vivo findings. ADMET properties, safety concerns, and formulation challenges are also evaluated to assess their translational potential. Overall, withanolides from W. somnifera demonstrate promising multi-target cardioprotective activity; however, further experimental and clinical studies are required to validate their safety and therapeutic efficacy in cardiovascular medicine.

INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of global morbidity and mortality despite significant advances in pharmacotherapy. Current therapeutic approaches, including ACE inhibitors, beta-blockers, statins, and antiplatelet agents, primarily target individual pathways and may not adequately address the multifactorial nature of cardiovascular disorders involving oxidative stress, inflammation, endothelial dysfunction, and metabolic imbalance.

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Medicinal plants and phytoconstituents have gained considerable attention as multi-target therapeutic agents due to their diverse pharmacological activities and favorable safety profiles. Among them, *Withania somnifera* (Ashwagandha), an important medicinal plant in Ayurvedic medicine, has demonstrated promising antioxidant, anti-inflammatory, adaptogenic, and cardioprotective properties.

The biological activity of *W. somnifera* is mainly attributed to withanolides, a group of steroidal lactones including withaferin A, withanolide D, withanosides, and sitoindosides. These compounds possess diverse pharmacological activities and have shown potential against several cardiovascular targets.

Recent advances in computational biology, particularly molecular docking and in silico ADMET prediction, have accelerated the evaluation of phytochemicals as therapeutic candidates. Several studies have reported favorable interactions of withanolides with cardiovascular-related proteins such as ACE, COX-2, eNOS, and inflammatory mediators. However, available evidence remains fragmented and lacks comprehensive integration with pharmacological findings.

Therefore, this review systematically summarizes recent studies (2020–2025) on the phytochemistry, molecular docking, pharmacological evaluation, and ADMET profiling of withanolides from *Withania somnifera* as potential multi-target cardioprotective agents.

2. PHYTOCHEMISTRY AND CLASSIFICATION OF WITHANOLIDES

2.1 Major Bioactive Withanolides

Withania somnifera contains several bioactive steroidal lactones collectively known as withanolides, including withaferin A, withanolide D, withanone, withanosides, and sitoindosides. Structurally, withanolides possess a C28 steroidal backbone with a characteristic lactone ring, contributing to their diverse biological activities.

2.2 Chemical Classification

Withanolides are classified based on oxidation pattern, side-chain structure, and glycosidic substitutions. Structural diversity among withanolides influences their polarity, lipophilicity, pharmacological activity, and molecular docking interactions.

2.3 Biosynthetic Pathway

Biosynthesis of withanolides in *W. somnifera* involves mevalonate and DOXP pathways, leading to sterol precursors that undergo oxidation, hydroxylation, and lactonization to form mature withanolide structures.

2.4 Pharmacophore Features

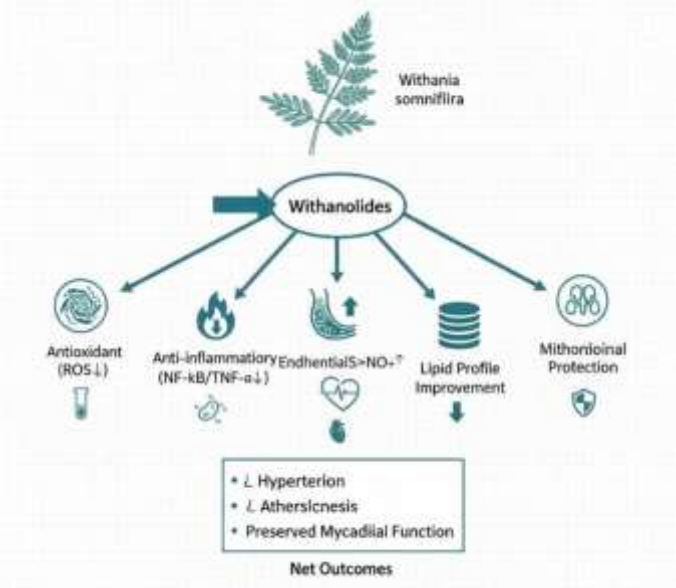
Key pharmacophoric features of withanolides include:

- Hydroxyl and carbonyl groups for hydrogen bonding
- Steroidal core enabling hydrophobic interactions
- Epoxide and lactone moieties important for target binding
- Flexible side chains facilitating protein interaction

These structural features contribute significantly to the cardioprotective and pharmacological potential of withanolides.

3. CARDIOPROTECTIVE MECHANISMS OF WITHANOLIDES

Withanolides from Withania somnifera exhibit cardioprotective effects through multiple mechanisms associated with cardiovascular disease (CVD). These include antioxidant activity, anti-inflammatory action, endothelial protection, lipid regulation, and mitochondrial stabilization. Experimental studies (in vitro, ex vivo, and in vivo) suggest that withanolides contribute to improved cardiovascular function and reduced oxidative stress.



3.1 Antioxidant and Free Radical Scavenging Actions

Oxidative stress contributes to endothelial dysfunction and atherosclerosis. Studies show that withanolides and Withania somnifera reduce oxidative damage by lowering MDA levels and enhancing antioxidant enzymes such as SOD, catalase, and GPx. Animal studies also demonstrate protection against doxorubicin-induced cardiotoxicity and myocardial injury, supporting their antioxidant-mediated cardioprotective effects.

3.2 Anti-inflammatory Effects

Withanolides, especially withaferin A, reduce inflammation by inhibiting NF-κB signaling and lowering cytokines such as TNF-α and IL-6. Studies also show reduced cardiac fibrosis and vascular inflammation.

3.3 Anti-stress and Neuroendocrine Modulation

Withania somnifera acts as an adaptogen that lowers cortisol and improves autonomic balance, helping reduce stress-related cardiovascular damage.

3.4 Lipid-Lowering and Anti-atherosclerotic Mechanisms

Ashwagandha extracts improve lipid profiles by lowering cholesterol, LDL-C, and triglycerides while increasing HDL-C. They also reduce lipid peroxidation and vascular inflammation.

3.5 Endothelial Protection and Nitric Oxide Modulation

Withanolides improve nitric oxide (NO) signaling, enhance vascular relaxation, and protect

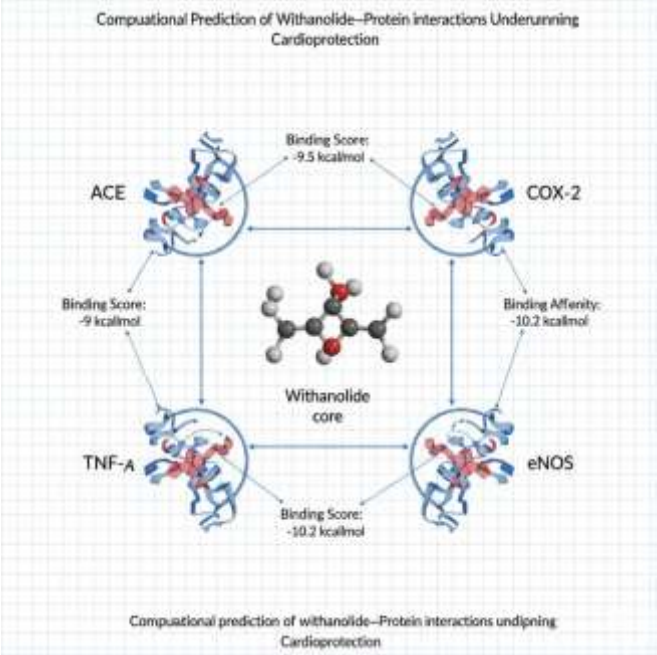
endothelial cells from oxidative damage, supporting cardiovascular health.

4. MOLECULAR DOCKING AND COMPUTATIONAL STUDIES OF WITHANOLIDES (2020–2025)

Molecular docking studies have highlighted the cardioprotective potential of withanolides from Withania somnifera. These compounds showed significant binding affinity toward cardiovascular targets such as ACE, COX-2, TNF-α, and eNOS, suggesting possible antioxidant, anti-inflammatory, and vasoprotective effects.

4.1 Summary of Docking Studies

Recent studies compared withanolides with standard inhibitors including captopril, celecoxib, and infliximab. Several compounds demonstrated favorable docking scores below −6 kcal/mol, indicating strong and stable target interactions.



4.2 ACE and ACE2 Docking

Withanolides A, B, and withaferin A showed strong ACE2 binding (−8.3 to −9.1 kcal/mol), involving His374, Glu402, and Asp405 residues (Kalra et al., 2021). Withanolide A also showed strong ACE binding (−9.4 kcal/mol), suggesting possible antihypertensive effects (Tambe et al., 2025).

4.3 COX-2 and LOX Docking

Withaferin A showed good binding with COX-2 (−9.2 kcal/mol), indicating anti-inflammatory potential (Ikram et al., 2024).

4.4 TNF-α Docking

Withaferin A strongly interacted with TNF-α (−10.1 kcal/mol), supporting inhibition of inflammatory pathways (Tambe et al., 2023).

4.5 eNOS and Nitric Oxide Pathways

Withanolide derivatives showed good affinity toward oxidative enzymes (−7.2 to −9.0 kcal/mol). Withanolide A also bound xanthine oxidase (−8.6 kcal/mol), suggesting antioxidant and endothelial protective effects (Chen et al., 2023).

4.6 Comparative Binding Summary

Target	Ligand	Score (kcal/mol)
ACE2	Withaferin A	−9.1
ACE	Withanolide A	−9.4
COX-2	Withaferin A	−9.2
TNF-α	Withaferin A	−10.1
Xanthine Oxidase	Withanolide A	−8.6

4.8 Experimental Interpretations and Limitations

Withanolides showed antioxidant, anti-inflammatory, and cardioprotective effects. However, evidence is mainly based on docking and animal studies.

Studies on *Withania somnifera* and withanolides suggest potential cardiovascular protective effects.

5.1 PRECLINICAL / ANIMAL STUDIES

Animal studies showed improved cardiac function, reduced oxidative stress, and lower cardiac injury markers in myocardial damage and cardiotoxicity models.

5.2 Human / Clinical Studies

Clinical studies suggest that *Withania somnifera* may improve cardiovascular and exercise-related parameters. In healthy volunteers, 330–500 mg/day of *W. somnifera* extract for 28 days improved physical performance and reduced systolic blood pressure during exercise compared to placebo, indicating possible vascular benefits.

5.3 Correlation Between Docking and Pharmacological Outcomes

Docking studies indicate strong binding of withanolides to cardiovascular targets (ACE, COX-2, TNF-α). Experimental studies also report antihypertensive, antioxidant, and anti-inflammatory effects. However, limited studies on isolated withanolides and lack of dose–response correlation restrict quantitative validation of these predictions.

5.4 Safety, Toxicity, and Pharmacokinetics

Ashwagandha and withanolides show low toxicity and are generally well tolerated. Pharmacokinetic studies indicate variable exposure, with only mild adverse effects reported.

5.5 Summary & Gaps in Evidence

Current studies support the cardioprotective, antioxidant, and anti-inflammatory potential of withanolides. However, evidence is limited by insufficient long-term clinical studies, low pharmacokinetic data, and lack of quantitative docking validation.

6. ADMET AND DRUG-LIKENESS EVALUATION OF WITHANOLIDES (2020–2025)

Recent in-silico studies suggest that major withanolides possess favorable drug-likeness, moderate lipophilicity, and acceptable ADMET properties, supporting their potential as cardiovascular drug candidates.

6.1 Physicochemical and Lipophilicity Parameters

SwissADME and Molinspiration analyses indicate that withanolides generally satisfy Lipinski's rule with suitable molecular weight, LogP, and hydrogen-bond parameters, suggesting good drug-like behaviour.

6.2 Absorption and Bioavailability

Withanolides show high gastrointestinal absorption (>85%) and good membrane permeability. Human LC-MS/MS studies (2024–2025) reported that a single 500 mg standardized

extract dose produced plasma CmaxC_{max}Cmax of 15–25 ng/mL within 1–2 h (TmaxT_{max}Tmax), indicating moderate oral bioavailability. Lipid-based and nanosuspension formulations improved absorption by 2–3 fold in animal studies.

6.3 Distribution and Protein Binding

Withanolides are moderately lipophilic (LogP ≈ 3) and distribute mainly into lipid-rich tissues. In-silico studies suggest withaferin A may cross the blood–brain barrier, while glycosylated analogs show limited permeability. Plasma protein binding is estimated to be >90%, contributing to low free plasma concentrations and slower clearance.

6.4 Metabolism and Biotransformation

Cytochrome P450 profiling indicates weak inhibition of CYP3A4 and CYP2C9, with minimal effects on CYP2D6 and CYP1A2. Predicted metabolism involves phase I oxidation and phase II conjugation (glucuronidation/sulfation), supported by metabolomics studies identifying hydroxylated and glucuronidated metabolites.

6.5 Excretion and Elimination Half-Life

Rodent pharmacokinetic studies report a terminal half-life of 4–5 h for withaferin A, mainly eliminated through biliary excretion. Human studies estimate a half-life of 6–7 h after oral administration, supporting twice-daily dosing of standardized extracts.

6.6 Toxicity and Safety Estimates

In-silico toxicity models classify withaferin A as a low-toxicity compound with an estimated LD50_{50}50 around 2,000 mg/kg in rodents. Sub-chronic rat studies (500–2,000 mg/kg/day for 28 days) showed no major toxicity or organ damage. No evidence of genotoxicity or mutagenicity was observed in Ames and micronucleus assays at nutraceutical doses.

6.7 Drug-Likeness and Pharmacophore Correlation

Withanolides showed acceptable drug-likeness (QED: 0.54–0.67) due to:

- Steroidal lactone scaffold
- Balanced H-bond properties
- Moderate polar surface area (≤100 Å²)

These features support target binding and membrane permeability.

6.8 Formulation Challenges and Strategies

Withanolides have low solubility and bioavailability. Improvement approaches include:

- Nanoemulsions/liposomes
- Phytosomes
- Cyclodextrin complexes

7. FUTURE PROSPECTS AND RESEARCH GAPS

Withanolides from Withania somnifera show promise for cardiovascular therapy due to multi-target activity. However, more translational and clinical studies are needed.

7.1 Need for Standardization

Major limitations include variation in:

- Phytochemical composition
- Plant part used
- Extraction solvent and method

Standardized extracts are essential for consistent therapeutic effects.

7.2 Role of Formulation and Delivery Systems

Poor solubility and low bioavailability remain key challenges. Strategies include:

- Nanoparticles/nanoemulsions
- Phytosomes/liposomes
- Cyclodextrin complexes
- Bioenhancers like piperine

These systems improve absorption and stability.

7.3 Integration with Network Pharmacology and AI

AI and network pharmacology can improve target prediction and multi-target docking studies of withanolides, supporting future drug discovery.

7.4 Translational Pharmacology

Clinical evidence for cardioproteive effects of withanolides is still limited. Future studies should focus on:

1. Disease-specific animal models
2. Biomarker-based clinical trials
3. PK–PD and dose optimization studies
4. Phase I–II cardiovascular trials

Collaboration between researchers and clinicians is essential for clinical translation.

7.5 Regulatory and Commercial Implications

Withanolides require standardized quality guidelines, validated bioassays, and regulatory approval for therapeutic use. Patent development and sustainable cultivation of *Withania somnifera* may support commercialization.

7.6 Research Gaps Summary

Domain	Gap	Direction
Standardization	Variable phytochemicals	LC–MS/NMR profiling
Bioavailability	Poor solubility	Nanocarriers, bioenhancers
Computational studies	Static docking	AI and MD simulations
Clinical translation	Limited human data	Clinical trials
Regulation	No standard framework	Global quality guidelines

7.7 The Road Ahead

From 2025–2030, integrated computational, formulation, and clinical research may help establish withanolides as potential cardioprotective agents.

8. CONCLUSION

From 2020 to 2025, significant progress has been made in understanding the cardioprotective effects of Withania somnifera and its withanolides. Studies suggest that compounds such as withaferin A, withanolide A, and withanolide D possess antioxidant, anti-inflammatory, and antihypertensive properties through interactions with targets including ACE, COX-2, TNF-α, and eNOS. Despite promising experimental findings, clinical application remains limited due to challenges related to standardization, bioavailability, and regulatory approval. Further research and well-designed clinical studies are needed to establish withanolides as evidence-based cardiovascular therapeutics.

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REFERENCES

1. Chong B, Jayabaskaran J, Jauhari SM, Chan SP, Goh R, Kueh MTW, et al. Global burden of cardiovascular diseases: projections from 2025 to 2050. Eur J Prev Cardiol [Internet]. 2025 Aug 25 [cited 2025 Nov 6];32(11):1001–15. Available from: https://dx.doi.org/10.1093/eurjpc/zwae281
2. Sulashvili N, Nimangre RR. MANIFESTATION OF SOME ASPECTS OF CARDIOVASCULAR DISEASES, IMPLICATIONS, PHARMACOTHERAPEUTIC STRATEGIES, EFFECTS, IMPACTS AND POTENTIAL HAZARDS IN GENERAL. JUNIOR RESEARCHERS. 2025 Feb 7;
3. Machín R, Florido M, … RCGEJ of, 2023 undefined. Adaptogenic Botanicals with Emphasis on Rhodiola rosea and Withania somnifera. researchgate.net [Internet]. [cited 2025 Nov 25]; Available from: https://www.researchgate.net/profile/Ruben-Machin/publication/377169443_Adaptogenic_Botanicals_with_Emphasis_on_Rhodiola_rosea_and_Withania_somnifera/links/65f1c943286738732d3e199d/Adaptogenic-Botanicals-with-Emphasis-on-Rhodiola-rosea-and-Withania-somnifera.pdf
4. White PT, Subramanian C, Motiwala HF, Cohen MS. Natural withanolides in the treatment of chronic diseases. Springer [Internet]. 2016 Sep 1 [cited 2025 Nov 20];928:329–73. Available from: https://link.springer.com/chapter/10.1007/978-3-319-41334-1_14?blog_tag=%27%27&blog_category=%27Blog%27%2C%27Digest%27
5. Kayesth S, Kumar Gupta K, Tyagi K, Mohan RR, Arora J, Nissapatorn V. Natural products and human health—A special focus on Indian Ginseng Withania somnifera (L.) Dunal. or.niscpr.res.in [Internet]. 2024 [cited 2025 Nov 25];15(2):244–59. Available from: https://or.niscpr.res.in/index.php/IJNPR/article/view/11665
6. Ghosh D, Antony B. Ashwagandha: Potential Drug Candidate from Ancient Ayurvedic Remedy [Internet]. 2025 [cited 2025 Nov 25]. Available from: https://books.google.com/books?hl=en&lr=&id=JDt-EQAAQBAJ&oi=fnd&pg=PT8&dq=Ashwagandha+is+an+interesting+candidate+for+cardioprotection+because+of+its+wealth+of+bioactive+compounds+and+its+history+of+use+for+thousands+of+years+in+a+number+of+traditional+systems+of+medicine+in+withanolides&ots=qRFSvYyXZl&sig=N6kh-Sk-_rMwRO6aZ25ScZlCenU
7. Ashwagandha VS, 2026 undefined. Adaptogens Unveiled: Ashwagandha's Multifaceted Role in Sports Nutrition and Mind-Body Health. taylorfrancis.com [Internet]. 2025 Aug 20 [cited 2025 Nov 25];305–10. Available from: https://www.taylorfrancis.com/chapters/edit/10.1201/9781032675961-25/adaptogens-unveiled-vanita-sharma
8. Gomes J. Benefits of Ashwagandha for Stress, Metabolic, and Immune Health. 2023 [cited 2025 Nov 25]; Available from: https://search.proquest.com/openview/10408f17d8ddc38c2d0114c99759433b/1?pq-origsite=gscholar&cbl=18750&diss=y
9. Misico RI, Nicotra VE, Oberti JC, Barboza G, Gil RR, Burton G. Withanolides and related steroids. Springer [Internet]. 2011 [cited 2025 Nov 19];94:127–229. Available from: https://link.springer.com/chapter/10.1007/978-3-7091-0748-5_3
10. SpringerOpen 2020 - Google Search [Internet]. [cited 2025 Nov 25]. Available from: https://www.google.com/search?q=SpringerOpen+2020&rlz=1C1UEAD_enIN1118IN11

20&oq=SpringerOpen+2020+&gs_lcrp=EgZjaHJvbWUyBggAEEUYOdIBCDQyMDZqMGo3qAIAsAIA&sourceid=chrome&ie=UTF-8

11. Design AHCCAD, 2021 undefined. Molecular docking, drug-likeness and ADMET analysis, application of density functional theory (DFT) and molecular dynamics (MD) simulation to the phytochemicals. benthamdirect.com [Internet]. 2020 Aug 5 [cited 2025 Nov 25];17(6):797–805. Available from: https://www.benthamdirect.com/content/journals/cad/10.2174/1573409916999200730181611
12. Logie E, Antioxidants WVB, 2020 undefined. Tackling chronic inflammation with withanolide phytochemicals—A withaferin a perspective. mdpi.com [Internet]. [cited 2025 Nov 25]; Available from: https://www.mdpi.com/2076-3921/9/11/1107
13. Tkaczenko H, Buyun L, … RKIJ of, 2025 undefined. Neuroactive Phytochemicals as Multi-Target Modulators of Mental Health and Cognitive Function: An Integrative Review. mdpi.com [Internet]. [cited 2025 Nov 25]; Available from: https://www.mdpi.com/1422-0067/26/18/8907
14. Silva-et-al-2025 | Request PDF [Internet]. [cited 2025 Nov 19]. Available from: https://www.researchgate.net/publication/389813178_Silva-et-al-2025
15. ResearchGate. - Google Search [Internet]. [cited 2025 Nov 25]. Available from: https://www.google.com/search?q=ResearchGate.&rlz=1C1UEAD_enIN1118IN1120&oq=ResearchGate.+++&gs_lcrp=EgZjaHJvbWUyBggAEEUYOTIGCAEQRRhA0gEJNDU5NmowajE1qAIIsAIB&sourceid=chrome&ie=UTF-8
16. Atteeq et al., 2022 in withanolides - Google Search [Internet]. [cited 2025 Nov 25]. Available from: https://www.google.com/search?q=Atteeq+et+al.%2C+2022+in+withanolides&sca_esv=22c7c7a659e0beaf&rlz=1C1UEAD_enIN1118IN1120&sxsrf=AE3TifMOJ0mGV0eKWBL7xM06IRzdBa2Hcw%3A1764015704309&ei=WL4kaZPAEqObseMP0cursAE&ved=0ahUKEwiTzLvLzouRAxWjTWwGHdHlChYQ4dUDCBE&uact=5&oq=Atteeq+et+al.%2C+2022+in+withanolides&gs_lp=Egxnd3Mtd2l6LXNlcnAiI0F0dGVlcSBldCBhbC4sIDIwMjIgaW4gd2l0aGFub2xpZGVzMgcQIRigARgKMgcQIRigARgKMgcQIRigARgKMgcQIRigARgKSJU-UIkDWMM4cAF4AZABAJgBmAKgAeMQqgEFMC4xLji4AQPIAQD4AQGYAgqgAqkRwgIHECMYsAMYJ8ICChAAGLADGNYEGEfCAgQQIxgnwgIGEAAYFhgewgILEAAYgAQYhgMYigXCAgUQABjvBcICBBAhGBXCAggQABiABBiiBJgDAIgGAZAGCJIHBTEuMS44oAfDJbIHBTAuMS44uAekEcIHBzAuNS40LjHIByg&sclient=gws-wiz-serp
17. Naturwissenschaftlichen D, Stein A. Withanolides: Elucidating steroidal lactone biosynthesis in Nightshades. 2022 [cited 2025 Nov 25]; Available from: https://repo.uni-hannover.de/handle/123456789/12957
18. Singh A, Raza A, Amin S, Damodaran C, Molecules AS, 2022 undefined. Recent advances in the chemistry and therapeutic evaluation of naturally occurring and synthetic withanolides. mdpi.com [Internet]. [cited 2025 Nov 25]; Available from: https://www.mdpi.com/1420-3049/27/3/886
19. Narayanan AK, Nagegowda DA. Biosynthesis of the triterpenoid withanolides in Withania somnifera. Curr Opin Plant Biol. 2024 Oct 1;81.
20. Pandey V, Ansari WA, Misra P, Atri N. Withania somnifera: Advances and implementation of molecular and tissue culture techniques to enhance its application. Front Plant Sci. 2017 Aug 9;8.
21. pharmacophore features relevant to docking i withanolides • Hydrogen bond donors and acceptors (e.g., hydroxyl, carbonyl groups) - Google Search [Internet]. [cited 2025 Nov 25]. Available from: https://www.google.com/search?q=pharmacophore+features+relevant+to+docking+i+withanolides+%E2%80%A2%09Hydrogen+bond+donors+and+acceptors+%28e.g.%2C+hydr

oxyl%2C+carbonyl+groups%29&sca_esv=742aa62f8b445c9b&rlz=1C1UEAD_enIN1118IN1120&sxsrf=AE3TifOOVgayoQzmFvuVCgNBwLRLXMCK0A%3A1764087989309&ei=tdglacbPEt-r4-EPgu2PyQw&ved=0ahUKEwiG_tHv242RAxXf1TgGHYL2I8kQ4dUDCBE&uact=5&oq=pharmacophore+features+relevant+to+docking+i+withanolides+%E2%80%A2%09Hydrogen+bond+donors+and+acceptors+%28e.g.%2C+hydroxyl%2C+carbonyl+groups%29&gs_lp=Egxnd3Mtd2l6LXNlcnAiggFwaGFybWFjb3Bob3JlIGZlYXR1cmVzIHJlbGV2YW50IHRvIGRvY2tpbmcgaSB3aXRoYW5vbGlkZXMg4oCiCUh5ZHJvZ2VuIGJvbmQgZG9ub3JzIGFuZCBhY2NlcHRvcnMgKGUuZy4sIGh5ZHJveHlsLCBjYXJib255bCBncm91cHMpSABQAFgAcAB4AJABAJgBAKABAKoBALgBA8gBAPgBAfgBApgCAKACAJgDAJIHAKAHALIHALgHAMIHAMgHAA&sclient=gws-wiz-serp

22. Jyothi MV, VL AB, Wagh VD, Rasheed A, Dayaramani R, Panigrahy UP, et al. Herbal Interactions with Cardiac Medications: A Comprehensive Review of Potential Interactions between Herbal Drugs and Commonly Prescribed Cardiac. benthamdirect.com [Internet]. 2025 [cited 2025 Nov 6];20(2):94–119. Available from: https://www.benthamdirect.com/content/journals/cds/10.2174/0115748863289321240424063819
23. Mohanty I, Arya DS, Dinda A, Talwar KK, Joshi S, Gupta SK. Mechanisms of Cardioprotective Effect of Withania somnifera in Experimentally Induced Myocardial Infarction. Wiley Online Library [Internet]. 2004 [cited 2025 Nov 26];94(4):184–90. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1742-7843.2004.pto940405.x
24. Gupta SK, Mohanty I, Talwar KK, Dinda A, Joshi S, Bansal P, et al. Cardioprotection from ischemia and reperfusion injury by Withania somnifera: a hemodynamic, biochemical and histopathological assessment. Mol Cell Biochem [Internet]. 2004 May [cited 2025 Nov 26];260(1–2):39–47. Available from: https://pubmed.ncbi.nlm.nih.gov/15228084/
25. Hamza A, Amin A, Daoud S. The protective effect of a purified extract of Withania somnifera against doxorubicin-induced cardiac toxicity in rats. Cell Biol Toxicol [Internet]. 2008 Jan [cited 2025 Nov 26];24(1):63–73. Available from: https://pubmed.ncbi.nlm.nih.gov/17520333/
26. Logie E, Berghe W Vanden. Tackling Chronic Inflammation with Withanolide Phytochemicals—A Withaferin A Perspective. Antioxidants 2020, Vol 9, Page 1107 [Internet]. 2020 Nov 10 [cited 2025 Nov 19];9(11):1107. Available from: https://www.mdpi.com/2076-3921/9/11/1107/htm
27. Vemuri V, Kratholm N, Nagarajan D, Cathey D, Abdelbaset-Ismail A, Tan Y, et al. Withaferin A as a Potential Therapeutic Target for the Treatment of Angiotensin II-Induced Cardiac Cachexia. Cells [Internet]. 2024 May 1 [cited 2025 Nov 26];13(9). Available from: https://pubmed.ncbi.nlm.nih.gov/38727319/
28. Akhgarjand C, Asoudeh F, Bagheri A, Kalantar Z, Vahabi Z, Shab-bidar S, et al. Does Ashwagandha supplementation have a beneficial effect on the management of anxiety and stress? A systematic review and meta-analysis of randomized controlled trials. Phytother Res [Internet]. 2022 Nov 1 [cited 2025 Nov 26];36(11):4115–24. Available from: https://pubmed.ncbi.nlm.nih.gov/36017529/
29. Visavadiya NP, Narasimhacharya AVRL. Hypocholesteremic and antioxidant effects of Withania somnifera (Dunal) in hypercholesteremic rats. Phytomedicine [Internet]. 2007 Feb 19 [cited 2025 Nov 26];14(2–3):136–42. Available from: https://pubmed.ncbi.nlm.nih.gov/16713218/
30. Pathak P, Shukla P, Kanshana JS, Jagavelu K, Sangwan NS, Dwivedi AK, et al. Standardized root extract of Withania somnifera and Withanolide A exert moderate vasorelaxant effect in the rat aortic rings by enhancing nitric oxide generation. J

Ethnopharmacol [Internet]. 2021 Oct 5 [cited 2025 Nov 26];278. Available from: https://pubmed.ncbi.nlm.nih.gov/34090907/
31. Guo R, Gan L, Lau WB, Yan Z, Xie D, Gao E, et al. Withaferin A Prevents Myocardial Ischemia/Reperfusion Injury by Upregulating AMP-Activated Protein Kinase-Dependent B-Cell Lymphoma2 Signaling. Circulation Journal. 2019 Jul 25;83(8):1726–36.
32. Chemistry SAAJ of, 2024 undefined. A Multi-Target mechanism of Withania somnifera bioactive compounds in autism spectrum disorder (ASD) Treatment: Network pharmacology, molecular. Elsevier [Internet]. [cited 2025 Nov 26]; Available from: https://www.sciencedirect.com/science/article/pii/S1878535224001746
33. Bashir A, Nabi M, Tabassum N, Afzal S, Ayoub M. An updated review on phytochemistry and molecular targets of Withania somnifera (L.) Dunal (Ashwagandha). frontiersin.org [Internet]. 2023 [cited 2025 Nov 6];14. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2023.1049334/full
34. Prabhakaran Y, Dinakaran S, … SMPJP, 2012 undefined. Molecular docking studies of withanolides against Cox-2 enzyme. researchgate.net [Internet]. [cited 2025 Nov 20]; Available from: https://www.researchgate.net/profile/Sathis-Dinakaran/publication/227397730_Molecular_docking_studies_of_withanolides_against_Cox-2_enzyme/links/5437ddfb0cf2027cbb205150/Molecular-docking-studies-of-withanolides-against-Cox-2-enzyme.pdf
35. Tambe et al. (2025) completed an analysis using network pharmacology in withanolides - Google Search [Internet]. [cited 2025 Nov 26]. Available from: https://www.google.com/search?q=Tambe+et+al.+(2025)+completed+an+analysis+using+network+pharmacology+in+withanolides&rlz=1C1UEAD_enIN1118IN1120&oq=Tambe+et+al.+(2025)+completed+an+analysis+using+network+pharmacology++in+withanolides&gs_lcrp=EgZjaHJvbWUyBggAEEUYOdIBCTcxODJqMGoxNagCCLACAQ&sourceid=chrome&ie=UTF-8
36. Prabhakaran Y, Dinakaran S, … SMPJP, 2012 undefined. Molecular docking studies of withanolides against Cox-2 enzyme. researchgate.net [Internet]. [cited 2025 Nov 26]; Available from: https://www.researchgate.net/profile/Sathis-Dinakaran/publication/227397730_Molecular_docking_studies_of_withanolides_against_Cox-2_enzyme/links/5437ddfb0cf2027cbb205150/Molecular-docking-studies-of-withanolides-against-Cox-2-enzyme.pdf
37. White PT, Subramanian C, Motiwala HF, Cohen MS. Natural withanolides in the treatment of chronic diseases. Springer [Internet]. 2016 Sep 1 [cited 2025 Nov 25];928:329–73. Available from: https://link.springer.com/chapter/10.1007/978-3-319-41334-1_14?blog_tag=%27%27&blog_category=%27Blog%27%2C%27Digest%27
38. Pathak P, Shukla P, Kanshana J, … KJJ of, 2021 undefined. Standardized root extract of Withania somnifera and Withanolide A exert moderate vasorelaxant effect in the rat aortic rings by enhancing nitric oxide generation. Elsevier [Internet]. [cited 2025 Nov 26]; Available from: https://www.sciencedirect.com/science/article/pii/S0378874121005237
39. Alam M, Abbas K, Iram F, Raza MT, Mustafa M, Zehra Z. Molecular Docking and Dynamics Studies of Withania somnifera Derived Compounds as GABA-A Receptor Modulators for Insomnia. Chronobiology in Medicine [Internet]. 2024 Jun 1 [cited 2025 Nov 26];6(2):77–86. Available from: http://www.chronobiologyinmedicine.org/journal/view.php?number=178&utm_source=chatgpt.com
40. Tambe MS, Shinde SR, Baheti AM, Nagar S, Pawar AT. Network pharmacology and in-silico studies for molecular mechanisms of analgesic, anti-inflammatory and anti-arthritic effects of Withania somnifera (L.) Dunal phytoconstituents. J Ayurveda Integr Med

[Internet]. 2025 Jul 1 [cited 2025 Nov 26];16(4). Available from: https://pubmed.ncbi.nlm.nih.gov/40578054/

41. Al-Eisa RA. A review on Selected Pharmacological and Phytochemical Activities of Ashwagandha (Withania somnifera). Egyptian Journal of Veterinary Sciences [Internet]. 2025 Feb 10 [cited 2025 Nov 26];0(0):1–23. Available from: https://ejvs.journals.ekb.eg/article_411012.html
42. Das M, Uppada S, Yukta R, Ranade A, Kumar S, Barthwal MK, et al. The Impact of Withania somnifera on Cardiovascular Health. Ashwagandha [Internet]. 2025 Aug 20 [cited 2025 Nov 19];264–79. Available from: https://www.taylorfrancis.com/chapters/edit/10.1201/9781032675961-22/impact-withania-somnifera-cardiovascular-health-milirani-das-sahitya-uppada-rana-yukta-anagha-ranade-sachin-kumar-manoj-kumar-barthwal-madhu-dikshit
43. Khalil MI, Ahmmed I, Ahmed R, Tanvir EM, Afroz R, Paul S, et al. Amelioration of Isoproterenol-Induced Oxidative Damage in Rat Myocardium by Withania somnifera Leaf Extract. 2015 [cited 2025 Nov 26]; Available from: http://dx.doi.org/10.1155/2015/624159
44. Hamza A, Amin A, Daoud S. The protective effect of a purified extract of Withania somnifera against doxorubicin-induced cardiac toxicity in rats. Cell Biol Toxicol [Internet]. 2008 Jan [cited 2025 Nov 26];24(1):63–73. Available from: https://pubmed.ncbi.nlm.nih.gov/17520333/
45. Usharani P, Fatima N, Kumar CU, Kishan P V. EVALUATION OF A HIGHLY STANDARDIZED WITHANIA SOMNIFERA EXTRACT ON ENDOTHELIAL DYSFUNCTION AND BIOMARKERS OF OXIDATIVE STRESS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED STUDY. International Journal of Ayurveda and Pharma Research. 2015;
46. Vaidya VG, Gothwad A, Ganu G, Girme A, Modi SJ, Hingorani L. Clinical safety and tolerability evaluation of Withania somnifera (L.) Dunal (Ashwagandha) root extract in healthy human volunteers. J Ayurveda Integr Med [Internet]. 2024 Jan 1 [cited 2025 Nov 26];15(1):100859. Available from: https://www.sciencedirect.com/science/article/pii/S0975947623001766
47. RK T, BA S, AU P, AA R, NN R. Effect of Withania somnifera on physical and cardiovascular performance induced by physical stress in healthy human volunteers. Int J Basic Clin Pharmacol [Internet]. 2016 Dec 21 [cited 2025 Nov 28];5(6):2510–6. Available from: https://www.ijbcp.com/index.php/ijbcp/article/view/42
48. Kim SK, Venkatesan J, Rathi P, Antony B. Pharmacokinetics and bioequivalence of Withania somnifera (Ashwagandha) extracts – A double blind, crossover study in healthy adults. Heliyon [Internet]. 2023 Dec 1 [cited 2025 Nov 26];9(12). Available from: https://pubmed.ncbi.nlm.nih.gov/38144272/
49. Choudhary B, Shetty A, Langade DG. Efficacy of Ashwagandha (Withania somnifera [L.] Dunal) in improving cardiorespiratory endurance in healthy athletic adults. Ayu [Internet]. 2015 [cited 2025 Nov 26];36(1):63. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4687242/
50. Puttaswamy N, Singh G, Mayachari A, Parameswaran M, Kudiganti V. Efficacy of Ashwagandha Extract Formulation (ASVAMAN®) on Improvement of Energy and Endurance: A Randomized, Double-blind, Placebo-controlled Clinical Study in Healthy Adults. European Journal of Medical and Health Sciences [Internet]. 2025 Apr 18 [cited 2025 Nov 26];7(2):88–93. Available from: https://www.ej-med.org/index.php/ejmed/article/view/2304
51. Lopresti AL, Smith SJ, Malvi H, Kodgule R, Wane D. An investigation into the stress-relieving and pharmacological actions of an ashwagandha (Withania somnifera) extract: A randomized, double-blind, placebo-controlled study. Medicine [Internet]. 2019 Sep 1 [cited

2025 Nov 26];98(37):e17186. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6750292/
52. Yadav DK, Kumar S, Saloni, Singh H, Kim MH, Sharma P, et al. Molecular docking, QSAR and ADMET studies of withanolide analogs against breast cancer. Drug Des Devel Ther [Internet]. 2017 Jun 22 [cited 2025 Nov 19];11:1859–70. Available from: https://www.tandfonline.com/doi/pdf/10.2147/DDDT.S130601
53. Letters YLP, 2022 undefined. In silico evaluation of pharmacokinetics and acute toxicity of withanolides in Ashawagandha. Elsevier [Internet]. [cited 2025 Nov 21]; Available from: https://www.sciencedirect.com/science/article/pii/S1874390021002706
54. Silva GW de S e, Marques AM, Sampaio ALF. Anticancer Effects of Withanolides: In Silico Prediction of Pharmacological Properties. Molecules. 2025 Jun 4;30(11):2457.
55. Letters YLP, 2022 undefined. In silico evaluation of pharmacokinetics and acute toxicity of withanolides in Ashawagandha. Elsevier [Internet]. [cited 2025 Nov 26]; Available from: https://www.sciencedirect.com/science/article/pii/S1874390021002706
56. Devkar S, Kandhare A, … BSJ of advanced, 2015 undefined. Evaluation of the bioavailability of major withanolides of Withania somnifera using an in vitro absorption model system. journals.lww.com [Internet]. [cited 2025 Nov 21]; Available from: https://journals.lww.com/japtr/fulltext/2015/06040/Evaluation_of_the_bioavailability_of_major.4.aspx
57. Singh SK, Valicherla GR, Joshi P, Shahi S, Syed AA, Gupta AP, et al. Determination of permeability, plasma protein binding, blood partitioning, pharmacokinetics and tissue distribution of Withanolide A in rats: A neuroprotective steroidal lactone. Drug Dev Res [Internet]. 2018 Nov 1 [cited 2025 Nov 28];79(7):339–51. Available from: https://pubmed.ncbi.nlm.nih.gov/30284738/
58. Dai T, Jiang W, Guo Z, Wang Z, Huang M, Zhong G, et al. Studies on oral bioavailability and first-pass metabolism of withaferin A in rats using LC-MS/MS and Q-TRAP. Biomed Chromatogr [Internet]. 2019 Sep 1 [cited 2025 Nov 26];33(9). Available from: https://pubmed.ncbi.nlm.nih.gov/31062367/
59. Patel SB, Rao NJ, Hingorani LL. Safety assessment of Withania somnifera extract standardized for Withaferin A: Acute and sub-acute toxicity study. J Ayurveda Integr Med [Internet]. 2016 [cited 2025 Nov 26];7(1):30. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4910650/
60. Jahagirdar S, Praveen Kumar H, Bhat SS, Poddar A, Chattaraj PK, Ahmad SF, et al. In silico evaluations of phytochemicals from Withania somnifera exhibiting anticancer activity against NADH-quinone oxidoreductase. journals.sagepub.com [Internet]. 2024 Jan 1 [cited 2025 Nov 21];43. Available from: https://journals.sagepub.com/doi/abs/10.1177/09603271241291399
61. Silva GW de S e., Marques AM, Sampaio ALF. Anticancer Effects of Withanolides: In Silico Prediction of Pharmacological Properties. Molecules [Internet]. 2025 Jun 1 [cited 2025 Nov 26];30(11):2457. Available from: https://www.mdpi.com/1420-3049/30/11/2457/htm
62. Saoji S, Rarokar N, Dhore P, … SDJ of DD, 2022 undefined. Phospholipid based colloidal nanocarriers for enhanced solubility and therapeutic efficacy of withanolides. Elsevier [Internet]. [cited 2025 Nov 23]; Available from: https://www.sciencedirect.com/science/article/pii/S1773224722001617
63. Devkar S, Kandhare A, Sloley B, Jagtap S, Lin J, Tam Y, et al. Evaluation of the bioavailability of major withanolides of Withania somnifera using an in vitro absorption model system. J Adv Pharm Technol Res [Internet]. 2015 Oct 1 [cited

2025 Nov 26];6(4):159. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4630722/

64. Ramapalaniappan A, Loganathan V, Morde A, Padigaru M, Patni P, Joshua L, et al. Superior Bioavailability of a Novel 1.5% Ashwagandha Formulation (ZenrootTM): A Randomized, Double-Blind, Single-Dose, Comparative, Oral Bioavailability Study in Healthy Adults. Adv Ther [Internet]. 2025 Oct 1 [cited 2025 Nov 26];42(10):4964–76. Available from: https://pubmed.ncbi.nlm.nih.gov/40748423/
65. Ivanović V, Rančić M, Arsić B, Pavlović A. Lipinski's rule of five, famous extensions and famous exceptions. Chemia Naissensis [Internet]. 2020 [cited 2025 Nov 29];3(1):171–81. Available from: https://www.researchgate.net/publication/371277639_Lipinski's_rule_of_five_famous_extensions_and_famous_exceptions
66. Waring MJ. Lipophilicity in drug discovery. Expert Opin Drug Discov [Internet]. 2010 Mar [cited 2025 Nov 29];5(3):235–48. Available from: https://pubmed.ncbi.nlm.nih.gov/22823020/
67. Dutra LL, Borges RJ, Maltarollo VG, Mendes TAO, Bressan GC, Leite JP V. In silico evaluation of pharmacokinetics properties of withanolides and simulation of their biological activities against Alzheimer's disease. Taylor & Francis [Internet]. 2024 [cited 2025 Nov 21];42(5):2616–31. Available from: https://www.tandfonline.com/doi/abs/10.1080/07391102.2023.2206909
68. Silva GW de S e., Marques AM, Sampaio ALF. Anticancer Effects of Withanolides: In Silico Prediction of Pharmacological Properties. Molecules [Internet]. 2025 Jun 1 [cited 2025 Nov 28];30(11). Available from: https://pubmed.ncbi.nlm.nih.gov/40509344/
69. Modi S, Tiwari A, Ghule C, Pawar S, Saste G, Molecules SJ, et al. Pharmacokinetic Study of Withanosides and Withanolides from Withania somnifera Using Ultra-High Performance Liquid Chromatography-Tandem Mass. mdpi.com [Internet]. [cited 2025 Nov 21]; Available from: https://www.mdpi.com/1420-3049/27/5/1476
70. Patel SB, Rao NJ, Hingorani LL. Safety assessment of Withania somnifera extract standardized for Withaferin A: Acute and sub-acute toxicity study. J Ayurveda Integr Med [Internet]. 2016 [cited 2025 Nov 28];7(1):30–7. Available from: https://pubmed.ncbi.nlm.nih.gov/27297507/
71. Dutra LL, Borges RJ, Maltarollo VG, Mendes TAO, Bressan GC, Leite JP V. In silico evaluation of pharmacokinetics properties of withanolides and simulation of their biological activities against Alzheimer's disease. J Biomol Struct Dyn [Internet]. 2024 [cited 2025 Nov 28];42(5):2616–31. Available from: https://pubmed.ncbi.nlm.nih.gov/37166375/
72. Dhar N, Razdan S, Rana S, Bhat WW, Vishwakarma R, Lattoo SK. of Molecular Understanding of Withanolide Biosynthesis and In vitro Studies in Withania somnifera (L.) Dunal: Prospects and Perspectives for Pathway Engineering. frontiersin.org [Internet]. 2015 [cited 2025 Nov 27];6(NOVEMBER):1–20. Available from: https://www.frontiersin.org/journals/plant-science/articles/10.3389/fpls.2015.01031/full
73. Ha JW, Yu JS, Lee BS, Kang DM, Ahn MJ, Kim JK, et al. Structural Characterization of Withanolide Glycosides from the Roots of Withania somnifera and Their Potential Biological Activities. Plants [Internet]. 2022 Mar 1 [cited 2025 Nov 27];11(6):767. Available from: https://www.mdpi.com/2223-7747/11/6/767/htm
74. AKILA RM, NITHIN MK. DESIGN AND EVALUATION OF ASHWAGANDHA CHITOSAN NANOPARTICLES FOR ENHANCED NEUROPROTECTION IN HUNTINGTON'S DISEASE. Int J Pharm Pharm Sci [Internet]. 2025 Aug 1 [cited 2025 Nov 27];64–8. Available from: https://journals.innovareacademics.in/index.php/ijpps/article/view/54517/32449
75. Yang L, Wang H, Zhu Z, Yang Y, Xiong Y, Cui X, et al. Network Pharmacology-Driven

Sustainability: AI and Multi-Omics Synergy for Drug Discovery in Traditional Chinese Medicine. Pharmaceuticals (Basel) [Internet]. 2025 Jul 1 [cited 2025 Nov 27];18(7). Available from: https://pubmed.ncbi.nlm.nih.gov/40732361/

76. Mohanty IR, Arya DS, Gupta SK. Withania somnifera provides cardioprotection and attenuates ischemia–reperfusion induced apoptosis. Clinical Nutrition [Internet]. 2008 Aug 1 [cited 2025 Nov 26];27(4):635–42. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0261561408001039
77. Sahoo N, Manchikanti P, Dey S. Herbal drugs: Standards and regulation. Fitoterapia [Internet]. 2010 Sep [cited 2025 Nov 28];81(6):462–71. Available from: https://pubmed.ncbi.nlm.nih.gov/20156530/
78. Wiciński M, Fajkiel-Madajczyk A, Kurant Z, Nutrients SL, 2024 undefined. Ashwagandha's Multifaceted Effects on Human Health: Impact on Vascular Endothelium, Inflammation, Lipid Metabolism, and Cardiovascular Outcomes—A. mdpi.com [Internet]. [cited 2025 Nov 6]; Available from: https://www.mdpi.com/2072-6643/16/15/2481

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