



CODEN [USA]: IAJPBB

ISSN: 2349-7750

**INDO AMERICAN JOURNAL OF  
PHARMACEUTICAL SCIENCES**<http://doi.org/10.5281/zenodo.3821354>Available online at: <http://www.iajps.com>

Review Article

**AN AYURVEDIC DRUG FOR TRUE INTEGRATION:  
THERAPEUTIC BENEFITS OF ASHWAGANDHA AND  
CURRENT STATE-OF-THE-ART.****Dr. Trupti Patil-Bhole\***

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**Article Received:** March 2020**Accepted:** April 2020**Published:** May 2020**Abstract:**

*Ashwagandha [Withania somnifera Dunal] is known for health benefits from thousands of years. Its therapeutic benefits can be dated back to most ancient Ayurvedic texts Sushrut samhita and Charaka samhita. The paper reviews ancient and latest state-of-the-art of this medicinal plant. This review focuses on traditional Ayurvedic methods of using Ashwagandha and its main formulations for various actions, mainly rejuvenator and life enhancing. It also review the current state-of-the-art , and promotes use of Ashwagandha as a integrative adjuvant for treatment of neuropsychological diseases, cancer, infertility and in sports medicine. In this paper, The most recent primary research from based on Ashwagandha were reviewed. Information from traditional ancient Ayurvedic classics have been reviewed in the paper with focus on the traditional formulations and efficacy. Articles from PubMed/ MEDLINE database published after 2017 till August 2019 have been selected. The unique methods of medicine formulations and extraction methods of Ayurveda are highlighted. Ashwagandha is a largely studied plant and its ethnopharmacological uses are justified by latest researches. True integration of Ayurveda and allopathic medicine is necessary for effective healthcare. Promising anti-cancer action of this herb justifies its benefits for integrative treatment. The traditional formulations of Ashwagandha are easy to prepare, easy to use and low on cost. The review highlights therapeutic potential of Ashwagandha, and highlights classical formulations.*

**Keywords:** Ashwagandha, Withania somnifera Dunal, Ayurveda, cancer, cardiorespiratory endurance, athletes, integration, integrative

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Please cite this article in press Trupti Patil-Bhole, *An Ayurvedic Drug For True Integration: Therapeutic Benefits Of Ashwagandha And Current State-Of-The-Art.*, Indo Am. J. P. Sci, 2020; 07(05).

**NARRATIVE REVIEW:****INTRODUCTION:**

Ashwagandha is a well-known Ayurvedic herb used single or in compounded form with other herbs. Ashwagandha consists of dried mature roots of *Withania somnifera* Dunal [Family Solanaceae], a perennial shrub, found in waste land, cultivated field and open grounds throughout India, widely cultivated in certain areas of Madhya Pradesh and Rajasthan in India, roots collected in winter and cut in short pieces [1]. Ashwagandha and its extracts are also used in preparation of herbal tea. It is a medicinal plant having health benefits like stress relieving, rejuvenator. It is a potential drug for integrative treatment of many disorders. In this paper the latest pharmacological studies have been reviewed. This article is also focussing on Ayurvedic view of application of this herb in clinical practise. Scientists have often found that the whole herb is synergistically more effective than the chemical derivatives [2].

**Pharmacopeial standards of Ashwagandha –**

The Ayurvedic Pharmacopoeia of India have elaborated the methods of identity, purity and strength as well as its main formulations and its actions [1]. Primary evidences support the

ethnopharmacological use of Ashwagandha, and we can consider it as a powerful medicine for true integrative management of many disorders.

**Traditional Ayurvedic methods of using Ashwagandha –**

Various traditional Ayurvedic formulae of Ashwagandha are available for clinical use. Though few classical uses of Ashwagandha have been reviewed previously [3], there is no elaboration of its main formulations with their classical indications and methods of consumption, as recommended by Ayurveda.

Ayurvedic treatment comprises of use of whole part of drug or many herbal drugs in combinations, in a holistic way. Use of accompanying media or adjuvants is a common way of drug delivery in Ayurveda. Concept of extracting the drug in various media is existent in Bhaishajyakalpana, the branch of Ayurved which deals with preparation of drugs. With this concept arrive many challenges in drug standardization. Ashwagandha has been mentioned as major ingredient in many classical formulations listed in table 1. Dose of its powder is generally regarded as 3-6 gms per day when in powder form [1].

**Table 1 : Elaboration of major classical formulations having Ashwagandha as major ingredient, formulation type, ingredients, dose in classical text & reference from authoritative Sanskrit texts of Ayurveda.**

Serial no.	Name of Classical formulation	Type of medicine	Ingredients and anupana [accompanying medicaments]	Medicinal use	Dose	Reference
1.	Kshar of Ashwagandha [Withania somnifera]	Kshar	Kshar of Ashwagandha, to be consumed with honey and ghee	For treatment of asthma	As per physicians advice	[4]
2.	Ashwagandha kshirapaka	Medicated milk for oral intake	Cow milk, Ashwagandha	Nourishing, weight gain, muscular growth	As per physicians advice	[5]
3.	Ashwagandha di leha	Instant leha	Sugar, Ashwagandha, Pippali, ghee, honey	For treatment of body wasting	As per physicians advice	[5]
4.	Ashwagandha ghritha prepared from milk cooked with Ashwagandha	Medicated ghee, to be consumed with milk and sugar, in morning	Ashagandha ghee is extracted from medicated milk [point no 3 in this table]	For treatment of body wasting	In morning	[5]
5.	Body scrub of Ashwagandha powder	Body scrub [dry powder] [udvartan]	With water	For treatment of body wasting	As per physicians advice	[5]

6.	Ashwagandha in form of powder or ghee, or potentiated powder	Ashwagandha in form of powder or ghee, or potentiated powder by levigating Ashwagandha powder by its decoction repeatedly.	With ghee and honey.	For strength, longevity of body	As per physician's advice	[6]
7.	Ashwagandha ghruta	Medicated ghee	Ashwagandha kwatha, kalka [paste], milk [Sneha siddhi by Ayurvedic process]	Vata shamak, aphrodisiac and muscle mass building action	As per physician's advice	[7]
8.	Ashwagandha di taila	Medicated oil for oral consumption, enema, external application over skin	Main ingredient is Ashwagandha.	Vata shamak, strengthening, muscle mass increasing, useful as aphrodisiac, treatment of male and female infertility	As per physician's advice	[8]
9.	Ashwagandha kshirapaka	Medicated milk	Decoction of roots of ashwagandha is boiled with milk and the milk is consumed after mixing ghee	Garbhadharan [treatment of female infertility]	To be consumed at ovulation period	[9]
10	Ashwagandha kshirapaka	Medicated milk	Ashwagandha, milk [process by Ayurvedic guidelines for making medicated milk], to be consumed with ghee, or oil and water	Body weight increasing and nourishing	15 days duration course	[10]
11	Ashwagandha kalka	Paste of roots	Paste of roots and warm water	Hrudayagata vata [heart disease]	As per physician's advice	[11]
12	Ashwagandha powder	Powder of roots	Roots of Ashwagandha	Hrudayagata vata [heart disease]	As per physician's advice	[11]
13	Ashwagandha powder	Powder of roots	With sugar and ghee	Insomnia	As per physician's advice	[11]
14	Ashwagandha powder	Powder of roots	With honey and ghee	Rejuvenator, anti-aging	40 gm daily for 1 month	[11]
15	Ashwagandha di Churna 1	Powder	Ashwagandha, Vriddhadaru [ <i>Argyria speciosa</i> ]	Aphrodisiac, rejuvenator, anti-aging	10 gm, with milk	[12]
16	Ashwagandha di Churna 2	Powder	Ashwagandha, Atasi [lin seeds], Shunthi [ <i>Zingiber officinalis</i> ], Nirgundi [ <i>Vitex negundo</i> ], Pippali [ <i>Piper nigrum</i> ], Aparajita [ <i>Clitoria ternatea</i> ]	Treatment of arthritis, rejuvenator, anti-aging affects	10 gm with milk	[12]

17	Ashwagandha di Churna 3	Powder	Ashwagandha, Shunthi [ <i>Zingiber officinalis</i> ], Pippali [ <i>Piper longum</i> ], Marich [ <i>Piper nigrum</i> ], Chaturjat [barks of <i>Cinnamomum zeylanicum</i> (dalchini), seeds of <i>Elettaria cardamomum</i> (elaichi), leaves of <i>Cinnamomum tamala</i> (tejpatra) and flowers of <i>Mesua ferrea</i> (Naga kesara), Bharangi [ <i>Clerodendron serratum</i> Linn], Talispatra [ <i>Abies webbiana</i> Lindl], Kachora [ <i>Curcuma zedoaria</i> ], Shweta jeerak [ <i>Cuminum cyminum</i> Linn.], Kaitarya [ <i>Myrica nagi</i> ], Jatamansi [ <i>Nardostachys jatamansi</i> ], Kankola [ <i>Piper cubeba</i> ], musta [ <i>Cyperus rotundus</i> ], Rasna [ <i>pluchea lanciolata</i> ], Kutaki [ <i>Picrorhiza kurrooa</i> ], Jivanti [ <i>Leptadenia reticulata</i> ], Kankushtha [ <i>Garcinia morella</i> ]	Useful to treat – diseases of Pitta predominance, giddiness, polyuria, weakness due to infection or injury, ascites, loss of appetite, gives strength	10 gms with sugar [10 gm]	[12]
18	Ashwagadhadi Churna 4	Powder	Ashwagandha , Guduchi [ <i>Tinospora cordifolia</i> ], Shatawari [ <i>Asparagus racemosus</i> ], Dashamula [ <i>Aegle marmelos</i> , <i>Gmelina arborea</i> , <i>Oroxylum indicum</i> , <i>Clerodendrum phlomidis</i> , <i>Stereospermum chelonoides</i> , <i>Desmodium gangeticum</i> , <i>Uraria picta</i> , <i>Solanum indicum</i> , <i>Solanum surattense</i> and <i>Tribulus terrestris</i> ], Bala [ <i>Sida cordifolia</i> ], Atibala [ <i>Abutilon indicum</i> ], Pushkarmula [ <i>Inula racemosa</i> ]	Kshaya [body wasting]	With milk.	[12]
19	Ashwagandha di Churna 5	Powder	Ashwagandha, Vriddhadaru [ <i>Argyrea speciosa</i> ]	Rejuvenator, anti- aging	With milk	[12]
20	Ashwagandha Kwatha	Decoction	Ashwagandha kwatha	Facilitates conceiving foetus	With ghee and milk, in morning	[12]
21	Ashwagandhar ishta	Medicated alcoholic drug	Ashwagandha, Musali [ <i>chlorophytum borivilianum</i> ], Manjishtha [ <i>Rubia cordifolia</i> ], Haritaki [ <i>Terminalia chebula</i> ], Haridra [ <i>Curcuma longa</i> ],	to treat unconsciousness , loss of memory, body wasting, mania, piles, loss of	2 months course. 20 ml dose	[13]

			Madhuka [ <i>Glycerhiza glabra</i> ], Rasna [ <i>Pluchea lanceolata</i> ], Vidari [ <i>Pueraria tuberosa</i> ], Arjun [ <i>Terminalia arjuna</i> ], Musta [ <i>Cyperus rotundus</i> ], Trivrut [ <i>Operculina turpethum</i> ], Ananta [ <i>Hemidesmus indicus</i> ], Shyama Trivrut [ <i>Operculina petaloidea</i> ], Sweta Chandan [ <i>Santalum album</i> ], Rakta Chandan [ <i>Pterocarpus santalinus</i> ], Vacha [ <i>Acorus calamus</i> ], Chitrak [ <i>Plumbago zeylanica</i> ], Dhataki [ <i>Woodfordia fruticosa</i> ], honey, Trikatu [ <i>Piper longum</i> , <i>Piper nigrum</i> , <i>Zingiber officinalis</i> ], Trijatak, Priyangu [ <i>Aglaia elaeagnoidea</i> ], Nagakeshar [ <i>Mesua ferrea</i> ].	appetite, vata diseases		
22	Ashwagandha di dhupa	Fumes of burnt mixture, for local exposure to anal haemorrhoids	Fumes of Ashwagandha, Nirgundi [ <i>Vitex negundo</i> ], Bruhati [ <i>Solanum indicum</i> ] and Pippali [ <i>Piper longum</i> ], ghee mixture	Pain due to haemorrhoids	As per physician's advice	[14]
23	Ashwagandha di Ghritam	Medicated ghee	Ashwagandha, milk, Ghee, trikatu [ <i>Piper longum</i> , <i>Piper nigrum</i> , <i>Zingiber officinalis</i> ], barks of <i>Cinnamomum zeylanicum</i> (dalchini), seeds of <i>Elettaria cardamomum</i> (elaichi), leaves of <i>Cinnamomum tamala</i> (tejpatra) and flowers of <i>Mesua ferrea</i> (kesara), etc	Diseases of vata-stiffness of jaw, arthritis, stiffness of waist, facial palsy, diseases of women related to childbirth, diseases related to Shukradhatu . aphrodisiac	Twice a day.	[15]
24	Ashwagandha ghrita	Medicated ghee for children	Ashwagandha, milk, ghee	Nourishing and strengthening for children and adolescents	As per physician's advice	[16]
25	Ashwagandha di taila	Medicated oil	Ashwagandha, Bala [ <i>Sida cordifolia</i> ], Laksha [ <i>Laccifer Lacca</i> ], Dadhimastu [water over curd], Manashila [realgar], Daruharidra [ <i>Berberis aristata</i> ], Renuka [ <i>Vitex negundo</i> ], Kushtha [ <i>Saussurea lappa</i> ], Musta [ <i>Cyperus rotundus</i> ], Chandan	fever, tuberculosis [abhyanga]	As per physician's advice	[17]

			[ <i>Santalum album</i> ], Haridra [ <i>Curcuma longa</i> ], Katuka [ <i>Picrorhiza kurrooa</i> ], Shatavha [ <i>Anethum graveolens</i> ], Murva [ <i>Marsdenia tenacissima</i> ], Devdar [ <i>Cedrus deodara</i> ], Manjishtha [ <i>Rubia cordifolia</i> ], Yashtimadhu [ <i>Glycyrrhiza glabra</i> ], Ushir [ <i>Vetiveria zizanioides</i> ], Sariva [ <i>Hemidesmus indicus</i> ]			
26	Ashwagandha di Nasyam	Nasal route of administration	Ashwagandha, rock salt [Himalayan salt], Vacha [ <i>Acorus calamus</i> ], Madhuka [ <i>Madhuca longifolia</i> ], Trikatu [ <i>Piper longum</i> , <i>Piper nigrum</i> , <i>Zingiber officinalis</i> ] and garlic [ <i>Zingiber officinalis</i> ], goats urine	For clarity of eyes.	-	[18]
27	Ashwagandha Paka	Semisolid, sweet, viscous medicine	Ashwagandha, Milk, Chaturjat [ <i>Cinnamomum zeylanicum</i> , <i>Cinnamomum tamala</i> , <i>Elettaria cardamomum</i> , <i>Mesua ferrea</i> ], Jatiphal [ <i>Myristica fragrans</i> ], Kesar [ <i>Crocus sativus</i> ], Vanshalochan [ <i>Bambusa arundinacea</i> ], Mocharas [ <i>Bombax malabaricum</i> ], Jatamansi [ <i>Nardostachys jatamansi</i> ], Chandan [ <i>Santalum album</i> ], Khadir Sar [ <i>Acacia catechu</i> ], Javitri [ <i>Myristica fragrans</i> ], Pippali and Pippalimula [ <i>Piper longum</i> ], Lavang [ <i>Syzygium aromaticum</i> ], Kankola [ <i>Pimenta dioica</i> ], Khsotasara [Walnuts], Bhallataka [ <i>Semecarpus anacardium</i> ], Shrungataka [ <i>Trapa bispinosa</i> ], Gokshur [ <i>Tribulus terrestris</i> ], Rasasindura, Abhrak Bhasma, Naga Bhasma, Vangabhasma, Loha Bhasma, sugar	Aphrodisiac, rejuvenator, nourishing, improves appetite  Prameha, jirnajwara, shosha, gulma, vata-pitta roga,	As per physician's advice	[19]
28	Ashwagandha Paka	Semisolid, sweet, viscous medicine	Ashwagandha, Shunthi [ <i>Zingiber officinale</i> ], Pippali [ <i>Piper longum</i> ], Marich [ <i>Piper nigrum</i> ], Twak [ <i>Cinnamomum zeylanicum</i> ], Ela [ <i>Elettaria cardamomum</i> ], Tamalpatra [ <i>Cinnamomum tamala</i> ],	Dyspnoea, coughing, indigestion, enlargement of spleen, mada, polyuria, rheumatism, inflammation,	20 gm [1/2 pala]	[20]

			Lavanga [ <i>Syzygium aromaticum</i> ], buffelo milk, honey, cow ghee, sugar	pain, piles, anaemia, jaundice, malabsorption syndrome, chronic obstructive jaundice, rejuvenates in one month, enhances growth of children, nourishing for women, increases breast milk, increases shukra, aphrodisiac.		
29	Ashwagandha di Lehyam	Semisolid, sweet, viscous medicine	Ashwagandha, sesame seeds, black gram, jaggery, long pepper [ <i>Piper longum</i> ], ghee	Strengthening effect	15 days consumption	[21]
30	Mashashwagandhadhi churna	Powder to be consumed with milk	Black gram, ashwagandha, Yashtimadhu [ <i>Glycyrrhiza glabra</i> ], Gokshura [ <i>Tribulus terrestris</i> ], green gram, ripe banana, to be cooked in milk and then dried, and added with sugar	Aphrodisiac	As per physician's advice	[22]
31	Balashwagandhadhi tailam	Medicated oil for local application etc [abhyanga et]	Ashwagandha, Bala [ <i>Sida cordifolia</i> ], Sesame Oil, Rasna [ <i>Pluchea lanceolata</i> ], Chandan [ <i>Santalum album</i> ], Manjishtha [ <i>Rubia cordifolia</i> ], Durva [ <i>Cynodon dactylon</i> ], Yashtimashu [ <i>Glycyrrhiza glabra</i> ], Karchurak [ <i>Curcuma zedoaria</i> ], Sariva [ <i>Hemidesmus indicus</i> ], Ushira [ <i>Vetiveria zizanioides</i> ], Musta [ <i>Cyperus rotundus</i> ], Kushtha [ <i>Saussurea lappa</i> ], Agarar [ <i>Aquilaria agallocha</i> ], Deodar [ <i>Cedrus deodara</i> ], Haridra [ <i>Curcuma longa</i> ], Kumudakanda [ <i>Nelumbo nucifera</i> ], Renuka [ <i>Vitex negundo</i> ], Shatavha [ <i>Anethum graveolens</i> ], Padmakesar [ <i>Nelumbo nucifera</i> ]	Strengthening, useful for treating fevers, psychosis, muscle, weakness, cough diseases of vata	As per physician's advice	[23]



32	Ashwagandha di Gana	Combination may be used as decoction or powder	Ashwagandha, Bala [ <i>Sida cordifolia</i> ], Dashamula [ <i>Aegle marmelos</i> , <i>Gmelina arborea</i> , <i>Oroxylum indicum</i> , <i>Clerodendrum phlomidis</i> , <i>Stereospermum chelonoides</i> , <i>Desmodium gangeticum</i> , <i>Uraria picta</i> , <i>Solanum indicum</i> , <i>Solanum surattense</i> and <i>Tribulus terrestris</i> ], Shunthi [ <i>Zingiber officinale</i> ], Grudhranakhi [ <i>Clitoria ternatea</i> ], Rasna [ <i>Pluchea lanceolata</i> ]	Treatment of vata vyadhi [disorders of vata dosha]	As per physician's advice	[24]
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### Formulations of Ashwagandha:

Ayurveda advocates the use of complete part of herb in holistic way, and not in form of pure extracted compounds. In Bhaishajyakalpana [Pharmaceutics and pharmacology of medicinal plant and animal products in Ayurveda] there is a concept of extractability of medicinal plants in different solvents. The extraction concept is not new; it is existence in ancient Ayurvedic literature.

1. Powder: Simplest formulation is the fine powder of dried roots of Ashwagandha. Leaves are also used in dried form. It is also the most commonly used form due to ease of administration.
2. Fresh roots- There is a recommendation in authoritative text Sharangdhar Samhita that for best results, Ashwagandha should be always used in fresh form by making juice or paste of its useful part, ie roots or leaves [25]. The fresh paste or juice may be used to formulate decoctions, medicated ghee etc.
3. Decoction- Decoction is important formulation used by practitioners of Ayurveda. Coarse powder of drug is heated with water and reduced before filtering. The water soluble phytoconstituents are extracted in decoction [kwatha].
4. Medicated milk- In formulations viz. kshirapaka [medicated milk], the paste of useful part of plant is cooked with equal amount or specific amount of milk and water, and the active ingredients may get extracted in lipid part of milk, and water. Such milk is a naturally nutritional supplement and also carries medicinal phytoconstituents [26].
5. Asawa and arishta are self-generated alcoholic medicines of Ayurveda. The active ingredients which have extractability in alcohol, are used in form of Ayurvedic Asawa and Arishtam. Fermentation is carried out with sugar or jaggery and flowers of *Woodfordia fruticosa*. Antioxidant activity of traditionally prepared Ashwagandharishta has been proved [27]. In an

in vitro and molecular study, histopathological parameters revealed restoration of normal tissue architecture by Ashwagandharishta, and hepatoprotection was evident through prevention of oxidative damage [28]

6. Awaleha : In complex formulations like awaleha there is involvement of decoction, sugar, powders, lipids [ghee and oils] etc. are formulated together in a systematic manner.
7. Medicated ghee and oils: Lipid soluble phytoconstituents are extracted in oil or ghee media. For alleviation of Vata element, lipids are necessary. Use of ghee and oil of Ashwagandha has been praised for treating painful disorders of Vata.
8. Leha- Instant leha is prepared by mixing powder of dried roots in ghee and honey to for a semisolid formulation.
9. Rasayan- In Rasayan adhyaya of Ashtangahridaya Uttartantra Rasayan Adhyaya there is reference of a formulation of single Rasayan drugs which include Ashwagandha. In this formulation, powder of single herbal drug Ashwagandha is levitated repeatedly with decoction / juice of same drug [known as *Bhavana*]and finally dried. This is concentrated form of Rasayan which is orally administered. [29]  
All these drugs are orally administered.
10. Nasya- Ashwagadhadi Nasya comprises of powder of ingredients, which is used through nasal route for inhaling [Pradhama Nasya]

Ayurvedic basic principles of formulation development are based on synergism and antagonism of desired and undesired effects, understood by properties of drugs and their physical composition.

Based on the desired drug targeting according to disease condition the best suited combination is selected by physician. Ashwagandha is known to pacify the basic body element 'Vata' [dosha], which



is one of three body elements 'Tridosha' described by Ayurvedic science [30]. It is the only body element which has speed and movement, and it is responsible for all functions which need pace and direction.

It is considered to be most crucial as it is responsible for all actions. Maximum diseases occur due to disturbance in the basic body element 'Vata'. Eighty diseases have been mentioned due to aggravation of Vata, where drug like Ashwagandha is useful. It is proven for promotive action, sleep induction, neurodegenerative disorders [31].

Ashwagandha is used as a household remedy by Indians, who consider it as the best tonic for old people and children, and as aphrodisiac by young people. It is one of the best nervine tonics of Ayurveda, the most ancient system of Medical Sciences [32].

The drugs which establish a balance of all body elements i.e. tridosha in body are most useful rasayan drugs. Generally, if taste of dravya is known; it is possible to predict its post-digestion effect and potency [hot or cold]. But in case of some Ayurvedic plant drugs these three attributes are not predictable and they are not logically related. For instance, generally drugs having Madhur taste have a cold potency. However; Ashwagandha possesses Tikta [bitter] and Kashay [astringent] taste [1] and yet ends up having madhura vipaka [anabolic effect] and ushnavirya [hot potency]. This makes it an ideal drug for treating disorders of Vata element. This concept is known as Vicitra Pratyayabdhha in Ayurved [33]. This plant shows promotive action in the body.

#### Primary researches on Ashwagandha –

Reverse pharmacology approaches of Withania somnifera leaves and roots have identified Withaferin A as the most bioactive compound for treatment of inflammatory ailments, supporting traditional use of their corresponding extracts in indigenous medicine [34].

On 17 August 2019, with the keyword 'Ashwagandha', 1116 articles were available on PubMed database. With the key words 'Ashwagandha' and 'stress', there were 224 articles enlisted on pubmed database. With the keywords as 'Ashwagandha', and 'antioxidant' there were 219 articles on pubmed database. With the keywords ashwagandha, anticancer there are 73 articles on pubmed database. With the keywords Ashwagandha, cancer, there are 237 articles were

available on pubmed database. Ashwagandha, and muscle as keywords yielded, 38 articles. Ashwagandha and sleep as key words yielded 15 articles. Ashwagandha and rejuvenation yielded 4 articles. Ashwagandha, and aphrodisiac as key words yielded 8 articles. Ashwagandha and depression as key words yielded 18 articles. Ashwagandha and arthritis as key words resulted in 32 articles. Ashwagandha and pain as key words fetched 25 articles. Ashwagandha and anxiety as key words yielded 32 articles, in the PubMed database search. The most recent papers from last 3 years were included for review.

#### Extraction of Ashwagandha -

Subcritical water extraction was applied to analyse the bio actives from Ashwagandha (*W. somnifera*) at varying temperature (100-200 °C) and extraction time (10-30 min). The effect of temperature and time has been investigated in terms of extraction yield, total phenolic content, cytotoxicity, antioxidant, and enzyme inhibitory activities. The withanosides and withanolides responsible for various biological effects were quantified using high performance liquid chromatography (HPLC). The HPLC analysis revealed Withanoside V, Withanoside IV, 12-Deoxywithastramonolide, Withanolide A, and Withaferin A as principle bioactive compounds in Subcritical water extraction, with high in concentration compared to microwave-assisted extraction, soxhlet extraction and maceration.

For Subcritical water extraction the highest extraction yield (65.6%; 200 °C for 30 min), total phenolic contents (82.5 mg GAE/g DE), antioxidant activity (DPPH: 80.3%, FRAP: 60.5% and ABTS: 78.9), and potent enzyme inhibitory effects were observed. The Subcritical water extraction and Withaferin A showed significant reduction in cell viability of cervical cancer (HeLa) cells, with IC50 values 10 mg/ml and 8.5 µM/ml, respectively but no cytotoxic effect for normal cells (MDCK). Thus, it has been reported that subcritical water extraction may provide effective extraction for Ashwagandha withanosides and withanolides compared microwave assisted extraction [MAE], Soxhlet extraction [SE] and maceration to conventional methods, which could be used for extraction of pharmacologically active fractions with therapeutic applications [35]. In Ayurveda, however traditionally whole plant parts are used and recommended as the phytoconstituents balance each other's actions so as to not harm the body.

Table 2 shows latest researches regarding various parts of Ashwagandha as pure herb powder as well as, its whole extracts; and only withanolides.

**Table 2- This table shows published evidences related to Ashwagandha from PubMed database, in last three years [Jan 2017- Aug 2019]**

Activity tested	Model/ method/ type of research	Drug / part used [of Ashwagandha]	Dose	Control used	Reference
Anti- cancer, [Inhibition of Ataxia telangiectasia and Rad3-related (ATR)]	In vitro, Human breast cancer cells	Withaferin A		Cisplatin	[36]
Inhibition of Non-alcoholic steatohepatitis (NASH), [hepatoprotective activity]	NASH models in mice -methionine-choline-deficient (MCD) diet and the 40 kcal% high-fat diet (HFD)	Withaferin A	Injected intraperitoneally (0.1 ml/20 g mouse), once per day	Vehicle [saline]	[37]
Prevention of neurodegeneration and cognitive impairments	In vivo rat model, LPS [Lipopolysaccharide-Induced Neuroinflammation]- rota rod test etc.	Ashwagandha leaf water extract (ASH-WEX)	4 ml per kg body weight, per oral [140 mg per kg body weight of leaf water extract of Ashwagandha]	Water as vehicle,	[38]
Stress resistance-promoting effect in mice in vivo	Foot shock stress-induced hyperthermia test, Marble-burying test	<i>Withania somnifera</i> root extract freed from withanolides (WFWS)	3.3 mg/kg, 10 mg/kg, 33.3mg/kg,100 mg/kg Once daily for 12 days	Stress control [vehicle treated], non-stress control [vehicle treated]	[39]
Anti-cancer activity [anti-tumour effect]	In vivo subcutaneous xenograft nude mouse model and in vitro assay HT-29 and HeLa cells	a folate receptor-targeting i-Extract nanocomplex (FRi-ExNC)- [Ashwagandha leaf-based nanomedicine]	50 mg Kg <sup>-1</sup> Body Weight) of i-Ex alone or encapsulated in nanocomplexes (i-ExNC and FRi-ExNC) through intraperitoneal injections	Saline as blank control	[40]
Cytotoxic [anti-cancer action]	MDA-MB-231 human breast cancer cells, MDA-MB-231 cells [In vitro]	a novel protein fraction, named here as WSPF, isolated from <i>Withania somnifera</i> roots		-	[41]
Neuroprotective effect against Bisphenol A (BPA) induced cognitive dysfunction and oxidative stress	Swiss albino mice, in vivo, in vitro	Extract of roots of WS , Soxhlet [600gm in 1000 ml]	100 mg/kg bw/day as pre-treatment for 1 week	Plain control	[42]
Anti-depression and anti-anxiety effect in persons with schizophrenia		Extract of <i>Withania somnifera</i>	1,000 mg of standardized WSE, for 12 weeks	Placebo controlled double blind	[43]

				clinical trial	
Inhibition of HIV diseases progression	CD38 expression on CD8 + T cells .	Withania somnifera root extract		-	[44]
Hepatocellular carcinoma [HCC] inhibition, [anti-cancer activity in HC]	cathepsin-D activation and DQ-BSA assays. Molecular study	Withaferin A		-	[45]
Effects on fatigue, vigour, and steroid hormones in aging, overweight males	A Randomized, Double-Blind, Placebo-Controlled, Crossover Study	ashwagandha extract, delivering 21 mg of withanolide glycosides a day	8 weeks	Placebo	[46]
Safety and pharmacokinetics study of WA in cancer patients	A phase I dose escalation study in patients with advanced stage high-grade osteosarcoma [13 patients]	Standardized root extract of W. somnifera containing 4.5% of WA w/w	72, 108, 144 and 216 mg of WA administered in two to four divided doses per day. (AshwaMAX 400), Each 400 mg capsule of AshwaMAX contained 18 mg of WA. The extract was processed in clarified butter as prescribed in Ayurveda.	Not used	[47]
Immunomodulatory and protective effects	zinc oxide nanoparticles mediated toxicity in Balb/c mice.	Withania somnifera extract and Withaferin A	28 days	-	[48]
Cytotoxicity for one or more of the four cancer cell lines used.	four human cancer cell lines (A549, SK-OV-3, SK-MEL-2, and HCT-15)	MeOH extract of W. somnifera roots combined with LC/MS-based analysis - identification of six new withanolides, withasilolides A-F (1-6), as well as seven known compounds	-	-	[49]
Anti cancer	transgenic and chemically-induced rodent models of breast cancer	Withaferin A		-	[50]

Ability to prolong morphine-elicited analgesia	molecular experiments in vitro		WSE (100 mg/kg, i.p.)	-	[51]
Treatment of airway inflammation.	effect of WA on ovalbumin (OVA)-induced airway inflammation in mice [in vivo]	Withaferin A		-	[52]
Anti-arthritis action	inflammatory cytokines such as Tumor Necrosis Factor (TNF)- $\alpha$ , IL-1 $\beta$ , IL-6 and IL-10 in CIA rats.	aqueous extract of Withania somnifera roots	Oral administration of WSAq at a dose of 300mg/kg.wt	Normal rats	[53]
Protection against high fat diet induced obesity	HFD-induced obesity through attenuation of hepatic inflammation, oxidative stress, insulin resistance in mice.	Withaferin A	1.25 mg/kg/day, for 12 weeks	-	[54]
Anti-scleroderma	28-day murine model of bleomycin-induced experimental scleroderma.	Withaferin A	Withaferin A administered at two doses 2 and 4 mg/kg intraperitoneally for 28 days.	-	[55]
Anti-inflammatory action in Acute pancreatitis	Cerulein-induced acute pancreatitis in mice [model]	Withaferin A	WA in intraperitoneal route, for 7 days	-	[56]
Regulation of cardiac ischemia reperfusion injury	therapeutic potential of WFA against cardiac ischemia reperfusion injury in vitro	Withaferin A	-	-	[57]
Amyotrophic lateral sclerosis (ALS) treatment	In vitro in mice [expressing G93A mutant form of superoxide dismutase (SOD1)]	WS extracts	WS extracts by gavage to mice)	-	[58]
Antioxidant and anti-diabetic potential	Streptozotocin (MLD-STZ) induced T1DM model	Withaferin A	(2 & 10 mg/Kg)	-	[59]
For treating exacerbation of schizophrenia	random-assignment, double-blind, placebo-controlled study	extract of Withania somnifera	1,000 mg/d) or placebo for 12 weeks	Placebo	[60]
Anti-tumour activity	In vitro cell study in CRC cells	Withaferin A	-	-	[61]
Anti-tubercular activity	A randomized, double-blind placebo-control study in two groups of 60 newly	W. somnifera root extract with DOT	8 weeks	placebo capsules and DOT	[62]

	diagnosed sputum smear positive pulmonary TB patients				
Prevention of neuroinflammation due to neuropathologies	In vitro model in rats	Water extract of Ashwagandha leaves	8 weeks, oral administration of drug, 140 mg/kg/day dry weight of ASH-WEX [leaf extract]	Normal diet	[63]
Treatment of male infertility	A triple-blind randomised clinical trial.	Withania somnifera root	5 gm daily [oral] for 90 days	Pentoxifylline 800 mg daily	[64]
Management of stroke	middle cerebral artery occlusion (MCAO) induced mitochondrial dysfunctions in experimental animal model of ischemic stroke.	Hydro-alcoholic root extract of WS containing 2% (w/w) Withanolides [Withaferin A and Withanolide A]	300 mg/kg (orally) for 30 days.	Sham control	[65]
Anti-leishmanial activity	in silico study - inhibition of <i>Leishmania donovani</i> dihydrofolate reductase-thymidylate synthase ( <i>Ld</i> DHFR-TS) enzyme	Withaferin A	-	-	[66]
Management of cachexia in cancer	Modulation in cytokines, antioxidants and apoptosis in leukaemic THP-1 cells and peripheral blood mononuclear cells (PBMC's).	aqueous extract of the root of <i>W. somnifera</i>	-	-	[67]
Anti-inflammatory activity	the human keratinocyte cell line HaCaT.	hot water extract of Ashwagandha roots	-	-	[68]
Antiproliferative activity	different human and murine cancer cell lines.	a standardized <i>W. somnifera</i> root extract (Viwithan)	-	-	[69]
Anti -chikungunya.	C57BL/6J in mice	amukkara choornam [A traditional polyherbal formulation of Ashwagandha]	-	-	[70]

Extension of lifespan in cancer	wild human EGFR-driven <i>C. elegans</i> model	Withanolide A	-	-	[71]
Anti-oxidant activity, apoptotic induction in hepatocellular carcinoma	HepG2 cells	Ashwagandha water extract	ASH-WX; 6.25 mg/ml-100 mg/ml)	-	[72]
Ability of WSE to influence MOP and NOP opioid receptors gene expression in SH-SY5Y cells	In vitro and in vivo experiments, molecular study	Withania somnifera Dunal roots extract (WSE)	-	-	[73]
Anti epileptic action [management of epilepsy] in temporal lobe affection	Molecular study	Withania somnifera (WS) root extract and withanolide A (WA)	-	-	[74]
Neuroprotection from cognitive dysfunction	human neuroblastoma cell line SK-N-SH against A $\beta$ peptide and acrolein in various cell survival assays.	Extract of WS	-	-	[75]
Anti -Alzheimer's disease (AD)	In vitro, in wistar rats	Withanone (WS-2), a compound isolated from root extract of <i>Withania somnifera</i>	orally/day to wistar rats for duration of 21 days	-	[76]
Attenuation of neuroinflammation associated with obesity	Rats, in vitro study	dry leaf powder of <i>W. somnifera</i> 1 mg/g of body weight	-	Normal	[77]
Cystostatic photo – [anticancer action]	Drug-Resistant and Drug-Sensitive Multiple Myeloma Cells.	Withanolide D; a steroidal lactone isolated from <i>Withania somnifera</i> roots	-	-	[78]
Neuroprotective in traumatic brain injury	Neurite growth in mice	<i>W. somnifera</i> root extract	-	-	[79]
Analgesic activity post operative	<i>Withania somnifera</i> root extract) in rat models of postoperative and neuropathic pain.	( <i>Withania somnifera</i> root extract)	<i>W. somnifera</i> root extracts (100 and 300 mg/kg).	-	[80]
Anti cancer	Osteosarcoma U2OS Cell Line	Withaferin A	-	-	[81]
Anti- hypothyroid activity	A prospective, randomized, double-blind, single-center	Ashwagandha root extract	600 mg daily	starch as placebo.	[82]

	placebo-controlled study				
Anti- cancer activity	human breast cancer cell-lines, MCF-7 and MDA-MB-231.	withaferin-A (WA)	-	-	[83]
Amelioration of nonclassic 11-hydroxylase deficiency	nonclassic 11-hydroxylase deficiency , a diagnosis found in elderly woman [78] presented with acne and male pattern alopecia [ case study in single patient ]	a standardized preparation of Ashwagandh a root,	400 mg twice daily, increased to 400 mg in morning & 800 mg in evening. Then increased to 800 mg twice daily.	-	[84]
Anti cancer in gastric cancer	gastric cancer cells	Withaferin A	-	-	[85]
Anti cancer [prostate cancer]	cell viability and cytotoxicity of <i>W. somnifera</i> extract in PC3 cells	Methanolic extract of <i>Withania somnifera</i> roots [Soxhlet ]	-	-	[86]
Antileishmanial and immunomodulatory activities	<i>in vivo</i> study in mice	F5 and F6 alcoholic fractions from <i>Withania somnifera</i> leaves and purified withaferin-A	F5 (25 and 50 mg/kg b.wt.), F6 (25 and 50 mg/kg b.wt.) orally, and withaferin-A (2 mg/kg b.wt.) intraperitoneally for 10 consecutive days	-	[87]
For healthy aging	stress induced HEK-293 cell line	Ashwagandh a compound	-	-	[88]
Neuroprotection in stroke	In silico analysis	<i>Withania somnifera</i> Phytochemicals	-	-	[89]

In the table only the most recent research articles from last 3 years were included, to highlight latest trends and evidences.

#### Anti- cancer activity:

Cancer has been the challenge to modern world, as one of the leading fatal disease. Efficacy of extracts and extracted compounds from Ashwagandha have yielded some evidences. The efficacy has been studied mostly in molecular studies involving various cancer cell lines.

Kim et al [85] studied efficacy of Withferin A and results indicate that the compound directly inhibits the proliferation and metastatic activity of gastric cancer cells, and suggest that Withaferin A may be developed as a drug for the treatment of gastric

cancer. It is reported that *W. somnifera* may be a good therapeutic agent in addition to the existing drugs for Prostate Cancer. Further studies with more prostate tissue samples are warranted [86]. Sudeep et. al. [69] have studied antiproliferative activity in various cancer cells and reported that Viwithan, a Standardized *Withania somnifera* Root Extract Induced apoptosis in murine melanoma cells. Yu et. al. [42] reported in vitro and in vivo evidence of Folic Acid Receptor-Mediated Targeting Enhances the cytotoxicity, efficacy, and selectivity of *Withania somnifera* leaf extract.

Ghosh et. al. [83] reported that Withaferin A induced impaired autophagy and unfolded protein response in human breast cancer cell-lines MCF-7 and MDA-MB-231. Hence it is known that Withaferin A may



be used as integrative drug for treating breast cancer. Hahm et al have reported that Withaferin A inhibited expression of ataxia telangiectasia and Rad3-related kinase and enhances sensitivity of human breast cancer cells to cisplatin [36]. An anti-cancerous novel protein fraction isolated from roots of *Withania somnifera* has been reported to induce ROS-dependent mitochondria-mediated apoptosis in human MDA-MB-231 breast cancer cells [41]. All these evidences came by in vitro studies. Clinical trials are needed to assess the clinical evidence of anti cancer action in breast cancer patient. Anti cancer activity of Withaferin A was assessed in transgenic and chemically induced rodent models of breast cancer [50], showing alterations in mitochondrial dynamics of cancer cells, and apoptosis of cells.

Zhang have reported that Withaferin-A Induced apoptosis in Osteosarcoma U2OS Cell Line via generation of ROS and disruption of mitochondrial membrane potential [81].

In a phase I dose escalation study in 13 patients with advanced stage high grade osteosarcoma, standardized root extract of *Withania somnifera*, Withaferin A was reported to have low oral bioavailability [47], and it showed 11 adverse events of grade 1 and grade 2 severity. The Ayurvedic methods of administration of Ashwagandha [table 1] comprise of natural bioavailability enhancers like black pepper and long pepper. The bioavailability of Ashwagandha formulations prepared by traditional Ayurvedic way may be superior to extracts.

Withaferin A has been tested in molecular study which indicated that in addition to inducing apoptotic cell death, Withaferin A also induced autophagy in hepatocellular carcinoma [45]. Anti-cancer activity of 6 withanolides was tested by studying cytotoxicity in 4 human cancer cell lines [A549, SK-OV-3, SK-MEL-2, and HCT-15) and it was concluded that withanolides exhibited cytotoxicity for one or more cancer cell lines [49]

It is reported that Withaferin A was tested for anti-tumor activity in an in vitro study in human colorectal cancer cells, and it showed dose dependent cytotoxic effect on the cells [61].

In another in vitro study to assess anti-cancer activity, aqueous extract of root of *Withania somnifera* exhibited modulation in cytokines, anti-oxidants and apoptosis in leukaemic THP -1 cells, and in peripheral blood mononuclear cells [67]. A standardised *W. somnifera* root extract has exhibited antiproliferative activity in different human and murine cancer cells [69]. Withanolide has been tested on wild human EGFR-driven C elegans model [71], shown to extend lifespan in cancer. Water extract of Ashwagandha showed promising anti-cancer action in HepG2 cells [70]. Withanolide D [

from roots of Ashwagandha] has exhibited cytotoxic effects in multiple myeloma cells [78].

The alcoholic extract of the dried roots of the plant as well as the so called active component withaferin A isolated from the extract showed significant antitumor and radiosensitizing effects in experimental tumours in vivo, without any noticeable systemic toxicity [90]

Given its broad spectrum of cytotoxic and tumor-sensitizing actions, *Withania somnifera* presents itself as a novel complementary therapy for integrative oncology care [91]

Ashwagandha has proved to be beneficial in cancer management in molecular and in vitro studies. More clinical studies are solicited for generating clinical evidence and benefit to maximum patients for anti-cancer action and also for enhancing quality of life. Withaferin A, from roots of Ashwagandha showed promising results in preclinical studies, and it has given future leads for further research [34]

#### Cardiovascular disorders –

A study highlighted the application of Withaferin A in cardiovascular diseases holding great promise for the future [57] as detailed in table 1.

Another recent study showed protective effect of *Withania Somnifera* pre-supplementation in ischemic stroke and are suggestive of its potential application in stroke management [65].

#### Sleep induction -

Triethylene glycol, an active component of Ashwagandha (*Withania somnifera*) leaves, is responsible for sleep induction [92]. There is concrete evidence about sleep induction activity exhibited by Ashwagandha.

#### Activities in neurological disorders -

It is reported that Ashwagandha should prove to be a potential therapeutic to halt the pathogenesis of Alzheimer's Disease, but further research is required [93]. Withanone showed promise in Alzheimer's disease treatment because of cognitive benefits and more importantly, mechanisms of action with respect to the fundamental pathophysiology of the disease, not limited to the inhibition of AChE, but also include the modification of A $\beta$  processing, protection against oxidative stress and anti-inflammatory effect [76]. Thus, multifunctional neuroprotective effect of withanone in alleviating cognitive dysfunction has been evident. It has been reported that ideally for prevention of Alzheimer disease, a treatment like medicinal food or a supplement that can be taken regularly without any side effect capable of reducing oxidative stress, stabilizing mitochondria, activating autophagy or proteasome, and increasing energy levels of neurons

would be the best solution [93]. A study put-forward *Withania somnifera* as potent drug candidate for BPA-induced cognitive impairment [43]. The extract of WS may prove to be effective therapeutic agent for suppressing neuroinflammation associated with various neurological disorders [38].

A reported study using in vivo and in vitro model systems provides first ever pre-clinical evidence that ASH-WEX can be used as a promising natural therapeutic remedial for the prevention of neurodegeneration and cognitive impairments associated with peripheral inflammation and neuroinflammation. [38]

The anti-aging drugs are worth special mention, considering the high prevalence of Alzheimer's diseases due to neuronal death due to aging [32]. Denosomin, Withanoside IV, Withanone, Denosomin, Sominone, Withanoside VI, Withanoside IV, Withanolide A have been linked with various known pharmacological actions in a review of utility of roots of Ashwagandha in neurodegenerative diseases [31]. These researches were either in vivo or in vitro studies. Ashwagandha and its constituents showed various activities against models of Alzheimer's disease and spinal cord injury [31]. Dry leaf powder of *W. somnifera* may prove to be a potential therapeutic agent to attenuate neuroinflammation associated with obesity and may prevent its co-morbidities as evident from an in vitro study in rat model [77]. The root extract has been tested and reported to be useful for improving memory and cognitive functions [94] in a prospective, randomized, double-blind, placebo-controlled study conducted in 50 adults. In this study, subjects were treated with either Ashwagandha-root extract (300 mg twice daily) or placebo for eight weeks.

#### Sports medicine -

*Withania somnifera* may be useful for generalized weakness and to improve muscular strength of legs, and eventually, the running speed of sportspersons [95]. Findings of a report suggested that Ashwagandha root extract enhances the cardiorespiratory endurance and improves quality of life in healthy athletic adults [96].

#### Infertility –

*W. somnifera* was reported to improve sperms parameters in idiopathic male infertility without causing adverse effects. [64]. This supports the ethnopharmacological use of Ashwagandha as a Vajikaran medicine. Intake of a standardized Ashwagandha extract for 8 weeks was associated with increased levels of DHEA-S and testosterone [46] in a clinical trial. The details are mentioned in table 1.

#### CONCLUSIONS:

In a nutshell it is concluded that *Withania Somnifera* has shown promising results for neurodegenerative diseases. It may prove to be effective for cancer management at all stages. It is a potent rejuvenator drug for health, physical and mental well-being. It may be used for integrative approach in sports medicine. It is a growth promoting drug in children, and may be used for enhancing weight and height of growing children. The main intention of this review is to encourage more rigorous clinical use of the medicinal plant Ashwagandha.

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