

## Psoriasis Vrs *Alstonia Scholaris*: Computational Validation as Functional Food

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### Abstract

Psoriasis is a skin disease. It is rare and is expanding worldwide. In this investigation the ion channel protein TRPV3 (Transient receptor potential cation channel, subfamily III) has been targeted vis-à-vis psoriasis, which is an important factor. Objective of this study was to find out *Alstonia scholaris*'s phyto compounds efficacy against psoriasis and use as functional food. The sun dried powder of the whole bark of medicinal plant *Alstonia scholaris* in capsule form of 450mg/cap as 'Functional Food' in Fixed dose and two phyto compounds (*Alstolenine* and (-) *Scholarine*) were taken from the mature tree's bark for in *Silico* investigation. Findings showed that functional food used recorded indicate near clear results with no toxicity. *In-Silico* molecular docking indicates *Alstolenine* as the champion with a binding affinity of -7.25 kcal/mol against the TRPV3 ion channel. It is also non-toxic. Synergistic with conventional therapeutics: vis-à-vis psoriasis. In conclusion, *Alstonia scholaris* bark as whole supports use as 'Functional Food'. *Alstolenine* posits as a good candidate for further 'Drug Discovery' related studies: vis-à-vis psoriasis.

### Keywords

Psoriasis; Functional Food, TRPV3 Ion Channel, *Alstonia Scholaris*, *Alstolenine*, Molecular Docking, Clinical Observation, In-Silico Study

## Introduction

Skin is the largest organ. And the one that also is (i) connected to the vital physiological process (ii) deep brain (iii) entire neuronal circuit (iv) experiences maximum weathering 24 x 7. Psoriasis and its variants are a chronic immune-mediated inflammatory skin disease. Initial variant can change during malady in-situ period with or without a nexus to small bone joints & tendons viz., psoriatic arthritis (metabolic pathways) and acute pruritus. Is acutely debilitating; disconcerting and inflicts deep psychological stress 24 x 7. Psoriasis can afflict any time, anyone. There are a few sub-variants as per clinical presentation. All are non-communicable; not vectorable; yet chance filial. Thus far every variant have failed curative efforts - century scale<sup>1</sup>. We have been searching new natural compounds vis-à-vis psoriasis<sup>2</sup> especially because there is no specific therapy<sup>3</sup>. In this transaction we have selected a natural plant namely *Alstonia scholaris* for our investigational study *Alstonia scholaris* belongs to the kingdom Plantae, genus *Alstonia* and *scholaris* species. It is full of medicinal properties. Traditionally it is used against various diseases. It has anti-diabetic, anti-inflammatory and anti-cancerous properties<sup>4</sup>. In this investigation two phyto-chemicals namely Alstolenine and (-) Scholarine are taken for in silico study against psoriasis<sup>5</sup>. Since 2012 we have been using the (whole) sun dried powder of the bark of *Alstonia scholaris*. Phytochemistry and pharmacology aspects of *Alstonia scholaris* has been studied extensively<sup>6</sup>. However, there is no study about the possibility of its use as 'Functional Food'. In this transaction we examine the theoretical aspect of molecular docking (*In-Silico*) and also present two unique cases (quinquennial best recorded case series) who consumed the same powder as 'Fixed dose - Functional Food'; were compliant and non-confounding.

## Pre Study Aboservation and Use

No pre use noted among tribal or distant communities. No folk medicine cue. Chance use in an extreme case (a railway station Tea vendor; year 2000) had resulted in abrupt swing change and promoted use to focus on *scholaris* as 'functional food'. Gradually numerous extreme severe cases got referred to us who all got 'abrupt-swing relief'.

## Objective

*Alstonia* is locally available, abundant & economic and no historical pre use report via-a-vis psoriasis. The objective therefore is to pursue the initial observation of its use as a 'Functional Food'. Also too ennoble the family physician and the community health care provider with final aim at 'drug discovery'.

## Materials and Methods

### *Gene selection for the study*

The genes 'Transient receptor potential' - cation channel, 'subfamily III' (TRPV-3) has been selected as it is the most involved in the patho-physiology of all psoriasis variants & stages<sup>7</sup>.

### *Phytochemicals of Alstonia Scholaris*

Phyto chemicals of *Alstonia scholaris* namely Alstolenine and (-) Scholarine are taken for the study. Table-1 enumerates the details. From PubChem database<sup>8</sup> the structure of Alstolenine and details structures were found. The 3d structure of the Alstolenine has been downloaded in SDF format and converted in .pdb format using Discovery studio tool<sup>9</sup> The details of (-) Scholarine was found from internet sources<sup>10</sup>. The smile is id taken for the development of 3d structure of this molecule. Using the Avogadro tool<sup>11</sup> the 3d-structure of Scholarine was developed and saved in pdb format. Figure 1 and 2 shows the 2D-structures of Alstolenine and Scholarine respectively.

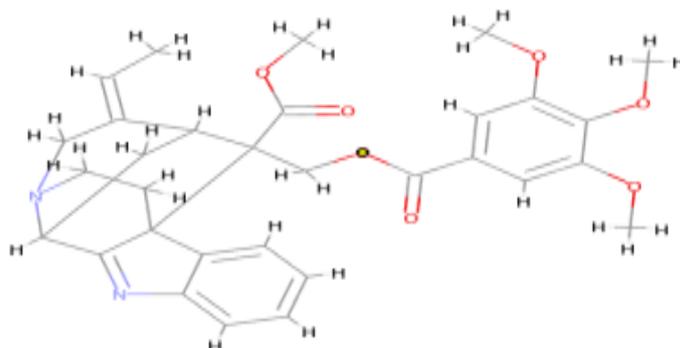


Figure 1: Alstolenine

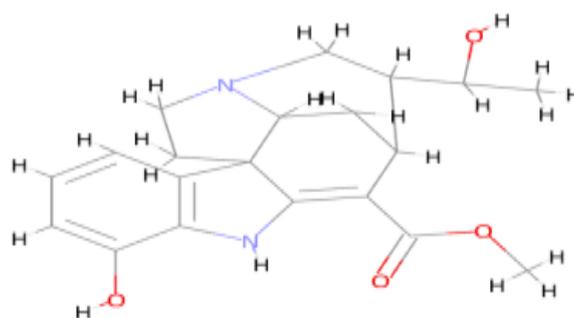


Figure 2: Scholarine

Table 1: Description of Phytochemical compounds present in *Alstonia scholaris*

SL. No.	Chemical name	Molecular formula	SMILE ID
1.	Alstolenine	C <sub>31</sub> H <sub>34</sub> N <sub>2</sub> O <sub>7</sub>	<chem>CC=C1CN2CCC34C5=CC=CC=C5N=C3C2CC1C4(COC(=O)C6=C(C(=C(C(=C6)OC)OC)OC)C(=O)OC</chem>
2.	(-)-Scholarine	C <sub>21</sub> H <sub>26</sub> N <sub>2</sub> O <sub>4</sub>	<chem>O=C(OC)C1=C2NC=3C(OC)=CC=CC3C24CCN5CC(C(O)C)C1CC54</chem>

#### Predicting of Binding Site

The binding site of TRPV3 was identified by Computed Atlas of Surface Topography of Proteins (CASTp)<sup>12</sup>. The consensus results depict the active site residues that take part in the binding site formation.

#### Molecular docking study of the two phyto-chemicals against TRPV3 protein of Psoriasis

Here the Autodock 2.3 tool has been used to dock the selected natural compounds against the TRPV3 protein<sup>13</sup>. AutoDock, is a well-known molecular docking tool that is widely used for the screening of compounds against potential targets.

### Toxicity checking

We have used the ProTox-II server<sup>14</sup>. for studying the toxicity of the selected compounds. Scholarine transpires comparatively as better. This is due to (the toxic) Methoxy anomer being associated with Alstolenine.

### Results

The gene TRPV3 is the most common and predominant in psoriasis. It is also involved in hyper-sensation and in psoriatic pruritus. Hence, TRPV3 has been taken for the study. The crystal structure of TRPV3's protein was collected from RCSB PDB pdb id 6dvz<sup>15</sup>. The chain A of the structure was selected for in silico investigation. From castp web server the binding site of the protein were obtained. The binding sites predicted of the protein are as follows: LYS 253, TYR524, THR937, ASP400, ASN401, GLU405, ILE406, VAL408, TYR 409, ASN410, THR 411, ASN412, ARG416, PHE 441, SER444, PHE447, TYR448, TYR451, TRP493, CYS496, ILE497, LYS500, GLU501, ILE503, ALA504, LEU507, LEU508, ARG509, PRO510, ASP512, LEU513, GLN514, SER515, ILE516, ASP519, ALA520, PHE 522, HIS523, PHE524, PHE526, PHE527, ALA564, TYR565, ARG567, LEU594, GLN695, ARG698, THR699, LEU701, GLU702, GLU704, LYS705 and MET706. The grid box value taken for the study is with X-dimension = 76, Y-dimension = 110 and Z-dimension =98 with spacing 0.375 Angstrom.

The two phyto-chemicals namely Alstolenine and (-) Scholarine got docked against the TRPV3 protein of psoriasis. Table 2 provides the docking results. Alstolenine shows the highest binding affinity of -7.25 kcal/Mol, ligand efficiency of -0.18 and inhibition constant of 4.88 $\mu$ m. And Scholarine has a binding affinity of -6.31kcal/Mol, ligand efficiency of -0.23 and inhibition constant 23.75  $\mu$ m, respectively. Alstolenine is indicated as Non-Toxic in and Scholarine as toxic in nature. Table 3 shows the results. Figure 3 and 4 represents the 2D and 3D -interactions of Psoriasis protein TRPV3 and- Alstolenine complex. Figure 5 and 6 represents the 2D and 3D -interactions of Psoriasis protein TRPV3 and - Scholarine complex.

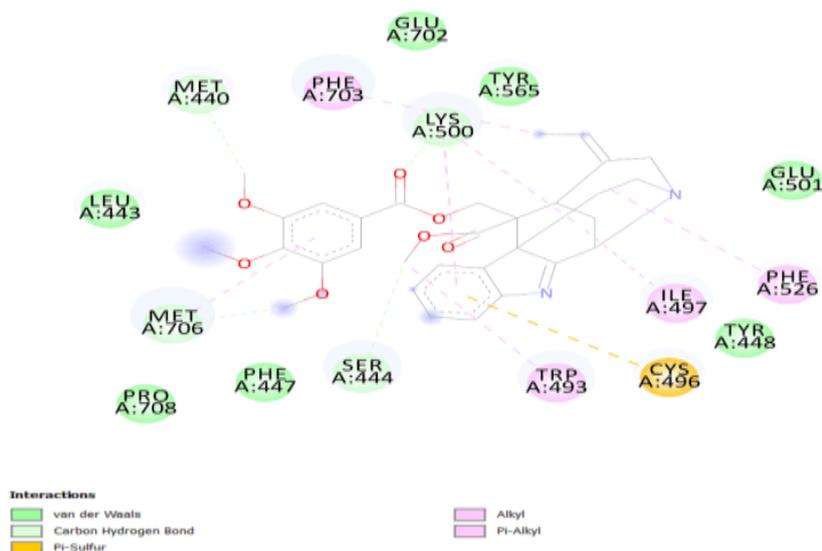


Figure 3: 2D interaction of Psoriasis protein TRPV3 and- Alstolenine complex

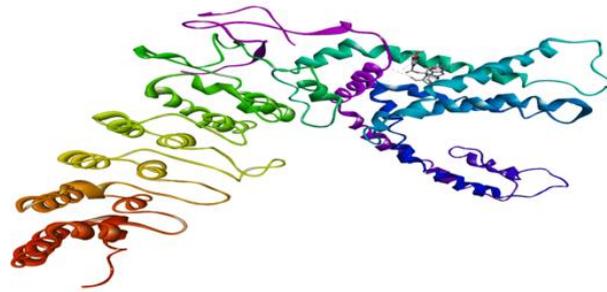


Figure 4: 3D interaction of Psoriasis protein trpv3 and - Alstolenine complex

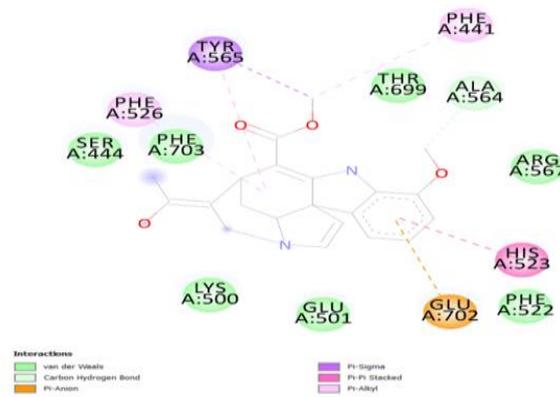


Figure 5: 2D interaction of Psoriasis protein trpv3 and- Scholarine complex.

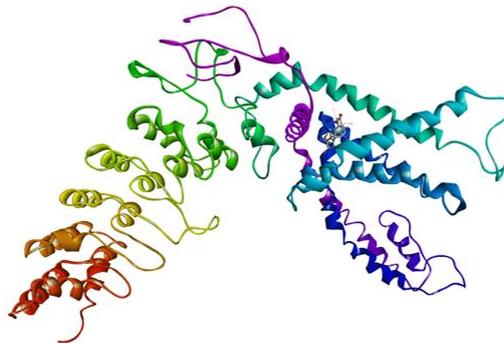


Figure 6: 2D interaction of Psoriasis protein TRPV3 and – Scholarine complex.

Table 2: Docking of screened Compounds from *Alstonia scholaris* against TRPV3 protein of Psoriasis

Sl. No.	Phyto-compound	Binding Energy(kcal/Mol)	Ligand Efficiency	Inhibition Constant ( $\mu\text{m}$ )
1.	Alstolenine	-7.25	-0.18	4.88
2.	(-)-Scholarine	-6.31	-0.23	23.75

Table 3: Toxicity of both compounds via protox-ii tool

S.N.	Phyto-compound	Tool	Toxic/Non-Toxic
1.	Alstolenine	ProTox-II	Non-Toxic
2.	(-)Scholarine	ProTox-II	Toxic

#### Functional Food Use

Whole bark of the mature *Alstonia Scholaris* was peeled (as large strands/pieces) from trunk using a curved machete; cut to smaller pieces; sun dried; crushed & pestelled to fine power (free flowing state). Forms a light brown powder of low bulk mass modulus. Long & excellent RT keeping property. The bark of the whole herb/tree permits easy peeling, after doing so it has to be grated and sun dried following which it becomes soft & brittle and can easily be hand ground. Can be orally ingested as 'Functional Food' @ 1gm per day.

#### Capsule Preparation

However, as it is extremely bitter and fixed dose in capsule form was also made by manually filling in empty transparent gelatin capsule shells of size No.'00' @ 450mg/cap for fixed dose application. Figure 7 represents the *Alstonias cholaris* plant and its dry form to capsule form.

#### Materials



Figure 7a



Figure 7b



Figure 7c



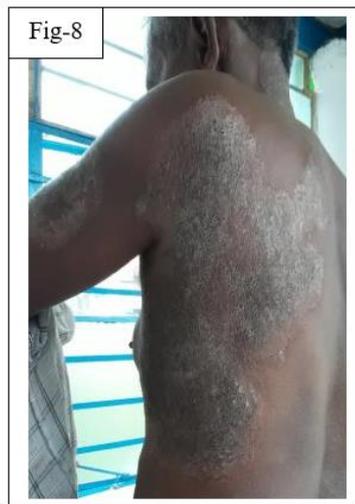
Figure 7d

Figure 7a is the tree *Alstonia scholaris*. Ornamental type abundantly used for avenue plantation; forms deep-cool shade. It is also abundantly available in the African; S American; Asian continents apart from Pacific rim nations. Figure 7b is the sun dried bark got from the steam of the mature tree. Figure 7c is

the ground powder of the bark hand filled in transparent cap shells of size '00' at 400mg/cap. Figure 7d is fresh piece of *Alstonia* bark.

### Case selection

Case 1 (Figure 8 and Figure 9) post mid aged; healthy; male. Catabolic threshold stage age. Not naïve – exposed to 4 years of multifarious therapies (including referrals to numerous medical colleges & National Apex institutions). No co-morbidity. Not on any other medicaments. No confounding. Fully compliant to our intervention.



### Dose

Severe, Chronic and Poly Pathology case (Case No. 1)

Photo (Figure 8) taken pre beginning *Alstonia* bark powder as functional food modality. Dose being 2 capsules at a time; 2 times per day (BD) at 12hr interval with water ad-libitum for initial 7 days. Thereafter, for next 7 days reduced to half. Thereafter, further tapered to 1/4<sup>th</sup> (i.e., 1 cap/day) for next 7 days and photo taken (Figure 9). Thereafter, further tapered to 1 cap on alternate day for next 7 days. Thereafter, further reduced to 1 cap every 3<sup>rd</sup> day (72hrs interval). After that functional food was withdrawn and patient advised to report monthly. No relapse within 3 months. Around 100<sup>th</sup> day there was signs of return of psoriasis. Patient was advised to continue at 1 cap/day post breakfast for 1 week per month for 3 consecutive months (i.e., 3 weeks of functional food support over 3 months' period = 21 capsules over 90 days). 1 year has passed. Status remains clinically clear. Patient is advised to continue a prophylaxis regimen at 1 cap/day post breakfast for 1 week every 3 months interval (7 capsules/90 days = 24 capsules over 1 year).

Note: The patient also had scabies as concurrent multi dermal pathologies ~ treated separately with 'Permethrin' post 45<sup>th</sup> day of initiation) and Clotrimazole lotion, alternatively for 2 days at a time with one-day wash down in-between the switch over.

Case 2 (Figure 10) showing juvenile, obese, anabolic, healthy male that exposed to 2 years of multifarious therapies. Co-morbidity – Juvenile obesity. Not on any medicaments. Fully compliant to our intervention. No confounding.



Figure 10a is right elbow and Figure 10b is left elbow. Photo taken pre beginning of Functional Food modality. Patient's status: male, obese, adolescent (20yrs), anabolic stage. Consent availed from patient & also parents. Apparent case of Pustular psoriasis.

#### *Dose*

Non Severe & Non Chronic case; Mono Malady (Case No. 2)

2cap at a time 2 times per day (BD) at 12hr interval with water ad-libitum for initial 5 days. Thereafter, for next 7 days reduced to half. Thereafter, wash down phase for 1 week (no medicine window). Then 'wash down' period of 7 days. Thereafter, Photo taken (Figure 11) of both elbows held together on 18th day of which 12 days were functional food intake period. Thereafter, Function Food support continued at 1 cap on alternate day. No confounding. No other medicaments taken or applied topically. Fully compliant. Plaque type of psoriasis. Significant positive results. Patient also reported loss of fatty feeling; more agile; and slackening of therapy existing of the tightness\rigidity in tender regions. Patient has been advised to continue a prophylaxis regimen at 1 cap/day post breakfast for 1 week every 3months interval (7 capsules/90 days = 24 capsules over 1 year).



Figure 11

### Supporting information (own data)

Psoriasis being well established as an auto-immune skin disease is marked by two major types at clinical presentation (i) intensifying plaque in inner regions –pruritus & chaffing; and (ii) acute erythematous necrolysis at the edges. The plaque size\domains (pain less) keeps enlarging while the erythema line and or the inter-regions migrate marked by burning sensation & mild pain (either major types do not respond to any known therapies). The erythema cum necrolysis is due to the host-pathogen phenomena. However, the host's own defence mechanism (being the pathogen/anti gen) topical and or internal medicines have thus far fallen short in outcome results. Our Functional food ostensibly: blocks signalling pathway; the auto-immune dermal disease/pathogenesis and thus down-turns excess dermis formation. Such 'functional food' is synergic with allopathic medicaments is also noted (in other cases – not presented). No confabulation. Between Scholarine and Alstolenine, pathology remission or clinical outcome results is better if the Alstolenine component or per dose can be raised. Scholarine (at sub clinical doses) also interdicts the auto-immune syndrome but is contra-indicated in loading doses especially in necrolytic & in erythematous types; and also in loading bolus doses (supporting information). Scholarine if given in loading doses for extended period results in pruritus in the erythematous or necrotic inter-regions (i.e., contra indicated). Therefore, short courses with Scholarine also yield therapeutic results. Interestingly, the plaque phenomena (and more especially severe and extensive plaque with layered chaffing) reacts well to a combination of Alstolenine and Scholarine moieties (whole herb) i.e. in severe plaque cases either moieties complement each other. Inter-alia methoxy group of toxic moieties posits as having a positive role in interdicting and\or un-plaguing. Immunity modulation is also hinted at.

Clinical validation of naïve Functional Foods is bedevilled with challenges & failures<sup>16</sup>; vis-à-vis psoriasis it is not noted. Our FF candidate due its systemic specificity has yielded presentable results. Haematological tests were done post 72hrs of cessation of last dose in all cases. All the parameters show normal reading. Slight reduction noted in LDL which was persistent & post prandial blood glucose which was transient. Cardiac tests also suggested a possible salutarious effect as much as stool & urine – routine test. CRP tests indicated a precipitous down turn and ESR tests indicated case specific variation (co-relation due).

Alstonine's fruit along with its seed has been in used in Ayurveda (Ref. 20-22) for dermal eruptions & pathologies. The seeds in-silico studies have also been done<sup>17</sup>. No studies about the use of bark has been reported.

Skin cancer's systemic genesis & bio mechanics is opposite of psoriasis. Inverse application of drugs results in acute exacerbation and even to malignancy<sup>18</sup>. Hence our choice herb is neither anti-cancer nor pro cancer. Psoriasis is predominant in the geo-domains limited between the tropics (tropo-equatorial). Tree *alstonia* along with all sister species are natural members cum abundant in the same geo-domain which are also comprise of economically weak cum developing nations also having most of the global sub-populations. All sister spp., contain bio-similar moieties that also have similar therapeutic effect on psoriasis (in-vivo). It is also thick leafed, deep shadow forming, evergreen floral member with sweet smelling winter blooming and strongly anti-bio film! Hence we have focused on this spp.

### Contribution of this study to the body of knowledge

Ayurveda (Indian National School of Medicine; 5000yrs heritage living school of medicine) mentions the use of this plant and its products vis-à-vis numerous dermal maladies<sup>19,20</sup> psoriasis is anecdotally included. It is mentioned as one of the APIs of any formulation with complex making process i.e. *Nighantu*<sup>21</sup>; and with hero-minerals i.e., Rasayan<sup>22</sup> *alias* not mono-use. Moreover, there is no study about its use as 'Functional Food'; as mono API, ion-channel affinity study. Also there is no computational study nor any clinical

demonstration thereof. This study adds the usefulness of the bark in caption domain. The bark in nature is abundant and renewable. Our approach in this communication is sharply psoriasis specific immune-modulation not effecting any other systemic or physiological processes (Novel).

Psoriasis the autoimmune chronic dermal disease. The causes being various including psychological, bacterial and virus<sup>23</sup>. It is associated with inflammation. The tropo-equatorial fruit Pomegranate and or its therapeutic moiety 'ellagic acid' - which is innate to gut and is very systemic, pregnancy safe - is a nice 'anti-inflammation functional food'<sup>24</sup>. Thus it can also be part taken internally, especially during the introduction (above enunciated therapy). However, acids cannot be topically applied.

#### *For Clinicians*

Functional food is versatile<sup>25</sup>. Clinicians do not have any standard operation procedure based therapy. Functional Foods permits the clinicians to alter doses frequently; try new formulations and specially drug therapies. Clinicians are also very concerned about pruritus as because any trail or experimental alteration chance leads to up-regulation of rim-region pruritus and even in exacerbation of the plaque regions. So synergist functional food permits a freer hand a better clinical basis<sup>26</sup>.

#### *SOS Nursing*

Psoriasis thus far has been left to the nurses<sup>27</sup>. In severe icterus a topical lotion or ointment having the following making process as follows. 1 gm of fine powder (or off load 3 capsules) suspended in surgical spirit for 1 hr., stir, decant the supernatant in glass or porcelain container add 1 pinch of KMNO<sub>4</sub>, mix, allow evaporation of 2/3 of the sprit. Soak sterile surgical absorbent cotton and apply via light contact. Optional to permit dress put on: After 1 hrs lightly or sparingly dust the same domain with a handmade thorough mixture of dry turmeric powder (9 parts v/v) and sulphur 1 part i.e., 1% v/v.

#### *Novelty – Therapeutics*

Internal use as fixed dose in powder form as aforesaid apart from use as FF. The lotion or cream intervention is of much value for the tourism industry viz., moist-sunny inland situations; sea-side and beach resorts.

#### *Drug Discovery*

- (1) The aforementioned averments are proto drug discovery – with clear & strong indicators. Ion channel based bonding posits as clinching, for it is specific.
- (2) (advanced Nano Tech application): A pill comprising 1:1 Alstolenine and Scholarine moieties w/w in the range of 100-200 mg of either moiety in the form of micro globules variably embalmed with acid resistant coat (for gastric pass) so that the moieties are made available in the alkaline mid-gut for efficient up-take; synergistic action with or without conventional medicines. Variable embalming will ensure delayed and extended release.

#### **Conclusion**

This 'functional food' (A Scholarine whole bark powder) indicates as broad spectrum in application character. Points in the short path to drug discovery. Pruritus wanes but remains in poly infection or infestation cases as in Fig. 8 & 9. Pruritus wanes almost entirely from all other clinical forms of psoriasis (Fig.10 (a,b) & 11). Alstonia scholaris's whole bark powder as a (complementing & supplementing, non-therapeutic) 'Functional Food' is likely to deliver knock out mechanism in psoriasis (with or without conventional medicaments). Possible use in talcum powder (unguent) industry & related benefits. It posits as best suited candidate in drug discovery studies vis-à-vis psoriasis and sister pathologies. Also, posits well

as having or no contradictions; with good likeness computationally, clinically promising other associated benefits viz., obesity; metabolic; etc. Hand make, Home make possible. Nursing possible. Fight Psoriasis at Home looms feasible. 1<sup>st</sup> time; Ground breaking; Nascent communication.

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