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Phytochemicals as new class of antibiotics to control Multi Drug Resistance

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Abstract: Phytochemicals represent traditional knowledge of compounds effective in symptomatic relief and potential healing properties. The idea has emerged from the fact that natural resources such as neem, turmeric, cloves etc. have been used to cure health problems since a really long time. Even in the current modern world, people have more preference towards natural therapeutics than modern drug formulations. Antibiotics are the drugs which are most easily prescribed unnecessarily to attain extremely rapid symptomatic relief. The practice has led to natural selection of resistant bacterial strains which are spreading at an alarming rate. The world without antibiotics is horrible to contemplate and can cause uncontrollable mortality rate in future due to resistant bacterial infections. The review elaborates importance of phytochemicals as compounds of natural origin, easy production, industrialization scope, broad spectrum antibacterial capabilities to tackle the crisis of antibiotics in the ever growing era of multi drug resistance

Keywords: Antibiotics, Bacterial infections, Multi drug resistance, Natural therapeutics, Phytochemicals

1. INTRODUCTION:

Over the past decades, much attention has been focused on traditional plants and their well known healing properties. Phytochemicals have been studied with great importance towards multi drug resistant gram positive and gram negative bacteria. Phytochemicals are defined as large group of chemical compounds derived from natural sources such as plants. These compounds represent decades of evolutionary existence essential for preventing their natural source from bacteria, fungi and viruses. These insights have been drawn to find potential therapeutics against bacterial infections.

Microbes rarely exist in pure isolated cultures, they are always found as complex consortium wherein they are metabolically supporting other form of bacterial cells. The coexistence of different types of bacteria create evolving environment for the cells to develop de novo processes and functions. The bacterial cells are capable of evolving their metabolic process to sustain themselves in almost any climatic conditions at any location. The motility of the bacterial cells enables them to spread from one location to the other leading to spread of infections. Infections caused by bacteria occur due to proliferation of virulent bacterial strains on or inside a living body. Bacterial cells can affect any part of the body causing severe consequences. The severe forms of bacterial infections include skin infections, food borne infections and sexually transmitted diseases. The present study elaborates severe bacterial infection diseases and role of phytochemicals as novel class of antibacterial agents has been proposed for the growing era of antimicrobial resistance.

1.1 Skin infections

Skin infections are not necessarily be always caused by bacteria, skin infections can be caused due to viruses, rickettsiae, fungi and parasites. However, ubiquitous presence of bacterial cells promotes skin infections faster and other microbes present in the surroundings. Primary skin infections have clinical course of disease progression, commonly caused by single pathogenic bacteria occurring over normal skin. These are mostly caused by *S. aureus*, *S. pyrogens* and coryneform bacteria. Secondary infections occur in an already diseased skin as a superimposed clinical condition. Clinical expressions of the diseases vary from one condition to the other. Most skin infections have characteristic observable signs of edema, severe inflammation, and fluid containing vesicles occurring on skin surface, lesions and furuncles with accumulated pus. These signs cause skin irritation and focal pain at the sight of inflammation or characteristic dermal abnormality.

Table 1: Classification of skin infections caused by different bacterial pathogens.

	Skin infection	**Clinical characteristics**	**Pathogen**
Primary infections	**Impetigo**	Thick lesions, dirty yellow crust with erythmatosus, lesions healing slowly and leaving scars	*S. aureus*, *S. pyrogens*
	Cellulitis	Inflammation of subcutaneous tissue	Streptococci group
	Scaled skin syndrome	Localized lesion	*S. aureus*
	Folliculitis	Follicular pustules	*S. aureus, Klebsiella pneumonia, Enterobacter aerogene*, *Proteus vulgaris, Propioniibacterium acnes*
	Pitted keratolysis	Pits coalescing to irregularly shaped areas of superficial erosion	Gram positive coryneforms
	Erythrasma	Burning and itching in pubis, toe web, groin, inframammary folds	*Corynebacterium minutissimum*
	Tricomycosis	Nodules in axillary and pubic regions	Corneybacterim species, lipophilic coryneforms
Secondary infections	**Interigo**	Heat, moisture and rubbing producing erythema	Overgrowth of transient bacteria
	Eczematoid dermatitis	Primary lesions, boil, draining ear/nose	*S. aureus*
	Toe web infection	Maceration, hyperkeratosis	Coryneform bacteria, *Brevibacterium*, Gram-negative rods

Other diseases	**Mycobacterial infection**	Lesions, chronic ulcers	*Mycobacterium tuberculosis, M. marinum, M. ulcerans*
	Actinomycetes infection	Lesions in cecum, appendix or pelvic organs	*Actinomyces israelii*

Natural therapeutic products and extracts from plants have been widely used as topical treatment for healing of wounds. Traditional therapeutic research has led the foundation for using medicinal plants in wound healing. A class of such therapeutic products is referred as phytochemicals, which react with oxygen groups and biomolecules to initiate therapeutic effects and treat human diseases [1]. Several research groups have shown that phytochemicals have the ability to treat critical inflammation based infections by promoting healing of severe wound and regeneration of dermal layer [2]. Wound healing is a multistep process involving regeneration, remodeling and neo-vascularization of dermal tissue. Phytochemicals such as curcumin has been proved to reduce burn pain and improve healing by analgesic and anti-inflammatory effect [3]. The escalated dose of curcumin (around 8000 mg/kg) has been studied beneficial in treating skin lesions without any cytotoxic effect. Curcumin has shown dermal protection by quenching free radicals, inhibiting NF-kB inflammatory response. It acts as angiogenic agent for wound repair by regulating *TGF-β* [4]. Other plant extracts such as picroliv, arnebin-1 have also shown wound healing effects with similar targets. Such phytochemicals can be used to treat tropical skin aberrations caused by microbial infections. Moreover, these phytochemicals can be coupled with antimicrobial agents to promote healing process in severe skin lesions occurring in microbial dermal infections.

1.2 Food borne infections

The correlation between food consumption and human diseases has been long for a long time. The food borne pathogens include bacteria, viruses, and parasites that cause illness in human body when ingested along with food. Food borne illness can occur in two forms, firstly when pathogen is present in food that is being ingested by the host (food borne infection); secondly when pathogens secrete toxins in food which when ingested cause illness (food intoxication). Bacteria are most prevalent pathogens associated with food borne diseases. Some bacteria form spores which are thermal resistant and make their way inside human body along with food. Most of these bacteria produce toxins inside the body leading to vomiting or diarrhea.

Campylobacter jejuni is one such gram negative bacteria responsible for mostly all food borne diseases in the US and Europe. *C. jejuni* infects 9.6 million people globally [5]. Tetracyclins and fluoroquinolones are common drugs used in *C. jejuni* infections, however, the bacterial cells have started evolving defense resistance meachanisms against these drugs. Plants containing flavanoids, rutin, quercetin, kaempferol have been studied as antimicrobial compounds. According to Dholvitayakhun et al., extracts of *Adenanthera pavonina* L., *Moringa oleifera* Lam. and *Annona squamosa* L. *Mammea africana* Sabine has been traditionally used for treating infections causing stomach pain and skin diseases in Africa [6]. Essential oils extracted from several plants have also shown potent antibacterial activities against *C. jejuni* [7][8][9].

Salmonella is another food borne pathogen belonging to family of Enterobacteriacea. Salmonella species has niche in gastrointestinal tracts of excreting organisms – humans, animals, birds. The ubiquitous presence of the organism is related with environmental pollution and reservoirs of humans' and animals' excreta [10]. The leading cause of food

borne disease called 'salmonellosis' is infection caused by *Salmonella* species. The transmission of species to human body is mostly originated from animals when humans consume animal products such as milk, eggs, meat. There are problems originating in treatment of the disease due to drug resistance occurring against antibiotics such as Ampicillin, Chloramphenicol. Fluoroquinolones have emerged out as resistant drug in case of salmonella infections [11]. A study conducted by Sadiq et al. explained use of *Acacia nilotica* L. extract against Salmonella species. The extract was showing antibacterial activity by disrupting bacterial cell wall and consequently releasing cellular constituents [12]. Further, Khan et al., confirmed the use of these extract for Salmonellosis treatment at minimum inhibitory concentration (MIC) as 9.75 µg/ml. Sugarcane baggase has also shown antibacterial activities against Salmonella [13] [14]. There are several other research studies displaying phytochemicals as remedies for bacterial infections. Thus with the growing cases of antimicrobial resistance, the research paradigm is shifting towards finding cues from traditional plant varieties, where phytochemicals have gained most attention.

Table 2: Phytochemicals studied on different food borne bacterial pathogens. The pathogenic species have developed resistance against common antibiotic drugs. Several phytochemicals have been studied as alternatives to target bacterial infections.

Species	Resistant Drugs	Effective Phytochemicals
Campylobacter species	Tetracyclins, fluoroquinolones	Flavanoids, kaempferol, quercetin, rutin, coumarin, carvacrol, cinnameldehyde, eugenol
Salmonella	Apmicillin, chloramphenicol, co-trimoxazol, fluoroquinolones	Sugarcane baggase, Entadanin, Aiton, Bolus,
Escherichia coli	Beta lactams, fluoroquinolones	Catechins, epigalactochatechins, procyanidins, flavonoids, anthocyanins, anthocyanidins
Staphylococcus aureus	Methicillin, Vancomycin	Clove, cress, lemongrass, rosemary, juglone
Shigella	Ampicillin, trimethoprim/sulfamethoxazole	Extracts of *Thymus vulgaris* L., *Thymus carmanicus* Jalas, *Zataria multiflora* Boiss., *Ziziphora clinopodioides* Lam. and *Ziziphora tenuior* L.
Listeria monocytogenes	Penicillin, Ampicillin, Tetracyclin and Gentamicin	cinnamaldehyde, carvacrol, thymol, Essential oils of *Zataria multiflora Boiss.* , *Carum copticum* (L.) *Benth.*, *Thymus capitatus* (L.), *Cymbopogon citratus* ,*Eryngium foetidum* L.
Clostridium spp.	Tetracycline	*Psidium guajava* L., *Haematoxylum brasiletto*, oils from *Satureja montana* L., berberine

Bacillus cereus	Penicillin, β-lactam antibiotics	*extracts of Rhus coriaria* L. and *Hipiscus sabdariffa* L.
Vibrio cholerae	Ampicillin, Nalidixic Acid, Nitrofurantoin, Cotrimoxazole	*extracts of Ocimum basilicum* L., *Opuntia ficus-indica (*L.) Mill., *Acacia farnesiana (*L.) Willd. and *Artemisia ludoviciana* Nutt

1.3 Sexually transmitted bacterial infections

The resistance towards antibiotics is not new in case of sexually transmitted infections (STIs), appearance of multidrug resistance is quite recent. Several bacteria have been leading cause of infections that can be sexually transmitted. Gonorrhea is one such STI caused by bacteria *Neisseria gonorrhea*, which tends to replicate in moist and warm regions of the body. The bacteria have recently developed resistance mechanisms against antibiotics like tetracycline and cephalosporins [15]. Gonorrhea is most common STI that majorly affects women and is a threat to health of neonatal, female fertility. Another prevalent bacterial infection Syphilis is caused by *Treponema pallidum* usually spread by sexual contact. The disease is characterized by painless sore in genitals, rectum or mouth and spreads when there is skin to skin contact or contact with mucous around the sores. Delayed treatment of syphilis can affect other organs of the body including heart, brain and can be life threatening. Although syphilis is commonly treated by single dose of penicillin but the organism has developed resistance against a spectrum of antibiotics including azithromycin, clindamycin, rifampin [16] [17] . Such reports of resistance towards antibiotics have rendered almost three quarters of the world to rely on traditional medicines for finding new therapeutics against these diseases.

According to various phytochemical investigations, therapeutic effects of plants and their extracts have been proved useful in treating STIs. Plant products such as apple cider vinegar, rosemary extract, garlic, tea tree oil, basil leaf extract, aloe vera, blueberries extract, eucalyptus oil have been successful in symptomatic relief in case of STIs. These plant extracts contain antibacterial properties and some of these boost immune system to fight against pathogenic bacteria. Interestingly, effect of plant based therapeutics has been preferential towards gram positive bacteria. Soma is another popular plant known for effective home remedies in STIs. Leaves, bark, root and fruits of the plant rich in saponins, have high pharmaceutical values in terms of anti-inflammatory and antibacterial properties beneficial in diseases like gonorrhea and syphilis [18]. Thus, plant based therapeutics and phytochemicals can be tremendous reservoir for identifying novel therapeutics against STIs. There have been several reports on specific therapeutic properties of plants and phytochemicals in regard to different sexually transmitted infections (Table).

Table 3: Plants used in treating urogenital tract infections and sexually transmitted infections (STIs). The plant parts such as leaf, root, bark have been analyzed in form of ointments and decoctions to induce anti-inflammatory and antibacterial effects [19].

Sexually Transmitted Infections	**Plant**	**Part of plant used**

Gonorrhoea	*Aloe ferox* Mill., Asphodelaceae, *Cassia occidentalis* (L.*), Cissus quadrangulis* L., *Polygala fruticosa* P. J., *Psidium guajava* L., *Terminalia sericea*	Leaf juice, decoctions, whole plant infusions
Syphilis	*Aloe ferox* Mill., *Euclea natalensis* A. DC., *Terminalia sericea*	Leaf juice, Leaf sap, root decoctions
STI related bladder pains	*Bowiea volubilis* Harv.	Decoction, poultice
Syphilitic sores, swollen testicles	*Cassia occidentalis* (L.)	Leaf/ seed/ root decoctions
Unspecified venereal diseases	*Psidium guajava* L., *Sansevieria aethiopica*, *Scabiosa columbaria* L., *Polygala fruticosa* P. J., *Psidium guajava* L.	Whole plant infusions, snuff infusions, ointment of charred roots
Problems related to genitalia	*Typha capensis* (Rohrb.)	Rhizomes/ root decoctions

2. ACTION MECHANISM OF PHYTOCHEMICALS

The mechanism of phytochemicals action has been based on macromolecular metabolism of bacterial cells. The widest variety of natural products target translation cascade affecting cell wall biosyntheses of bacterial cells. The major pathways targeted by phytochemicals cause protein synthesis inhibition, transcription inhibition, replication inhibition including prevention of cell division, dysfunctioning of ion uptake, RNA processing and inhibition of DNA methylation [20] [21] [22]. The major positive aspect of phytochemicals is that these represent mixture of several compounds with alternative targets inclusing cell wall, metabolism, and protein synthesis in bacterial cells. These compounds can target one process or have the capability to show synergistic effects on different mechanisms. Considering the fact of synergism, the phytochemicals hold potential for targeting broad spectrum of bacteria and it is most likely that their antimicrobial activity can be attributed to more than a single mechanism of action (Table 4). The synergy of phytochemicals can further be explored in combination with reduced concentration of antibiotics to control resistance in remaining antibiotics.

Whenever natural products research is concerned, enthopharmacology and toxicology have been two major fields of concern. The acceptance of natural therapeutic to be used as drugs requires elucidation of exact mechanism of action of phytochemicals and other natural therapeutics. The strong hold on such clarity will expand the scope of antimicrobials discovery to synthesize potent and effective therapeutic drugs and antibiotics. However, most of the studies described till now have sufficient *in-vitro* data, but *in-vivo* studies are required for proving their applicability to humans without toxic effects. Further studies are required from pharmacokinetic and toxicological aspects of natural extracts and phytochemicals.

Table 4: Class of phytochemicals and their bacterial targets. Phytochemicals represent broad classes of chemical compounds originated from natural sources having metabolic targets for broad spectrum antibacterial effects [23].

Class of phytochemicals	**Description**	**Examples**	**Antibacterial target studies**
Alkaloids	Organic nitrogenous bases	Strychnine, emetine, brucine, piperine, caffeine, quinine, emetine, brucine	*Staphylococcus aureus* (MRSA), *Streptococcus sanguinis, Actinobacillus pleuropneumoniae, Pseudomonas aeruginosa, S. epidermidis*
Sulfur-containing phytochemicals	Organosulfur compounds	Glucosinolates from broccoli, cabbage, cauliflowers, sulforaphane, isothiocyanates (berteroin, hirsutin, phenethyl-isothiocyanate, alyssin and erucin)	*S. mutans, S. sobrinus, Lactobacillus casei, S. aureus, Enterococcus faecalis, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Prevotella nigrescens, Clostridium perfrigens Candida albicans, Helicobacter pylori*
Terpenoids	Isoprene based cyclic compounds	Thymol, carvacrol, eugenol, transcinnamaldehyde, β-resorcylic acid, vanillin, thymol, berberine, eugenol, cinnamaldehyde	*Salmonella typhimurium* and *L. monocytogenes, S. typhimurium, Mycobacterium tuberculosis, A. baumannii, S. aureus, E. faecium, S. enterica*, or *P. aeruginosa*
Carotenoid	Class of tetraterpenoids	carotenoid fractions from red paprika, Valencia orange peel, Rose hips, peel of Shation Pummelo	*B. subtilis, E. coli, S. aureus, B. cereus, B. amyloliquifaciens, B. magaterium, Proteus vulgaris* and *S. typhy*.
Polyphenols	a large group of compounds found in many fruits, vegetables and legumes	galangin, kaempferol, quercetin, myrecetin, galangin,	*K. pneumonia, S. pyogenes, S. haemolyticus, Xanthomonas vesicatoria, H. pylori, S. mutans*

3. ANTIMICROBIAL RESISTANCE – PHYTOCHEMICALS CAN SOLVE THE CRISIS OF ANTIBIOTICS

Antimicrobial resistance (AMR) is a natural phenomenon of bacterial evolution amplified by inappropriate uses of antibiotics. When bacterial cells are exposed to same antibiotics for

prolonged period of time, natural mutations occur in their metabolic processes which help them escape from antimicrobials and make treatment of bacterial infections obstinate and extremely difficult. According to a report of Centre for Health Protection, Department of Health (Hong Kong), there is misunderstanding on indications of antibiotics and doctors have been mistaking cold and flu as conditions treatable with antibiotics [24]. The government launched "Antibiotic Stewardship Programme in Primary Care" in 2017, to prevent unnecessary prescription of antibiotics and emergence of antimicrobial resistance. The drug resistance of India has been 71% as reported by The Centre for Disease Dynamics, Economics and Policy. Th global threat can cause 10 million deaths by 2050 costing to 66 trillion euros of health care services [25]. Thus it is the need of the hour to start digging the traditional antimicrobials research for discovering a new class of antibiotics for future.

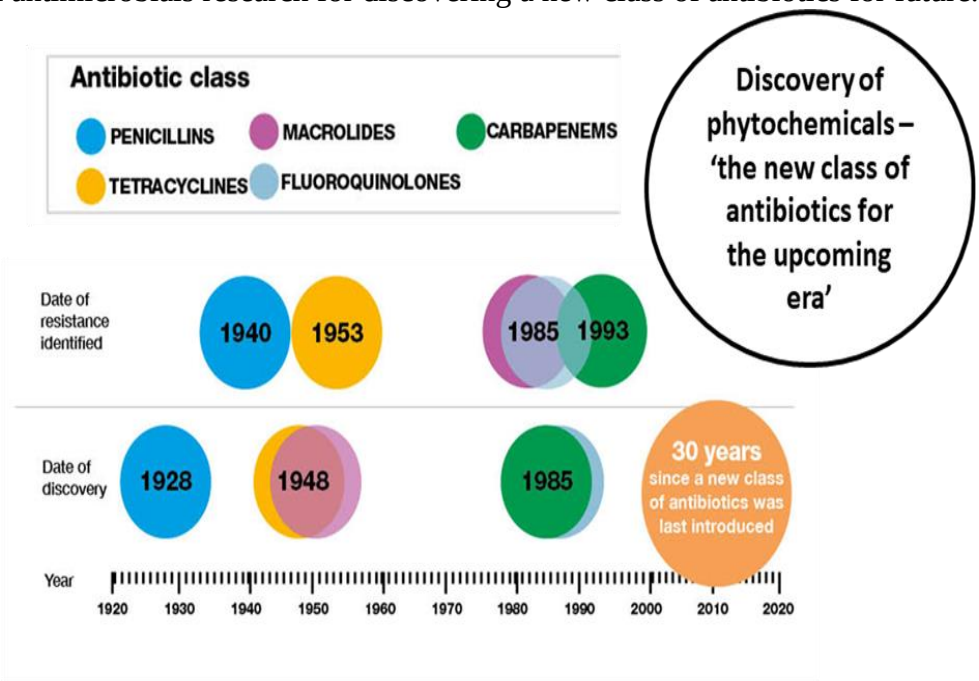

Figure 1: Antibiotics discovery and resistance timeline. The most common antibiotics have been rendered ineffective in research studies for their effect on bacterial pathogens. Antibacterial phytochemicals can be a new class of antibiotics for the growing era of antimicrobial resistance. (Image modified from Public Health England).

The first case of antibiotics resistance has been as old as 1928 for the first antibiotics discovered – penicillin. Since then, the resistance apocalypse has been increasing exponentially encompassing common antibiotics such as cephalosporins, carbapenamns, macrolids, tetracyclins etc. it has been 30 years since a new class of antibiotics has been introduced. Referring to traditional research, phytochemicals are potential therapeutic agents for treating bacterial infections. The mechanism of action needs to be specifically devised for acceptance of natural phytochemicals based therapeutics in the drug market.

4. CONCLUSION

The world is dealing with the crisis of antimicrobial resistance, which has encompassed the rate of discovery of pharmaceutical antibiotics. The resistance against drugs is most common in bacterial cells due to their rapid adaptation mechanisms and their ability to survive in adverse conditions. The situation has created an undeniable need for discovery of new class of antibiotics. The traditional knowledge of natural products' implications in healing and

symptomatic relief has been explored to arrive at the class of phytochemicals. These phytochemicals have shown promising antibacterial effects against multi drug resistant gram positive as well as gram negative bacteria. The phytochemicals have shown positive results when studied for complex bacterial infection related diseases including skin infections, food borne pathogens and sexually transmitted infections. The gap of thirty years since the discovery of novel antibiotics class, provides scope for phytochemicals to capture the market as pharmaceutical ingredients. The positive aspects of natural origin, easy production, industrialization scope and broad spectrum effect can make the phytochemicals next boom in antibiotics drug market. The review elaborates importance of different phytochemicals, their antibacterial capabilities and market demand to tackle the crisis of antibiotics in the ever growing era of antimicrobial resistance.

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