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Biopesticides: A healthy alternative of hazardous chemical pesticides, current development and status in China

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Abstract
To provide the safe and healthy food to the increasing world population in China and all over the world, the development of modern research based scientific system of organic farming is a dire need of time. Fertilizers, high yielding crop varieties and use of chemicals are key tools to ensure plentiful supply of high yielding agriculture products in China. To cope with these issues, quick and easy use of synthetic chemicals is creating several problems such as, severely health hazardous chemicals on food, environmental pollution and residual effects in land and water resources. In addition, to overcome pesticides resistance in insects, pest resurgence, secondary pest outbreak, the biologically safe and environment friendly pesticides are utmost needed. So, in current system biopesticides are good alternatives of chemical agro-inputs which are less toxic to health, ecofriendly, target specific, biodegradable, suitable for integrated pest management tool, non-phytotoxic and are easily implemented in organic farming. Biopesticides production in China is increasing rapidly by the interest of government and China's plan of zero growth of pesticides consumption to 2025. This is the key plan of biopesticides production and development to replace health hazardous chemical pesticides in China and world together. Hence, this article reviews the present status of health friendly biopesticides development and formulation for future prospects in China as healthy alternative of hazardous synthetic chemicals.

Introduction

Health hazardous impacts of synthetic/chemical pesticides on different organisms

To provide a continuous, healthy and safe food is the real target of a society in civilized world. When we think quantitatively, the production of abundant food requires the use of different agrochemicals such as chemical soil fertilizers, synthetic plant growth hormones, weedicides, insecticides, fungicides, nematicides, bactericides, antiviral chemicals etc. these chemicals are useful in production of valuable food crops, but they cause serious harm to the human, animals, and beneficial insects and cause serious diseases and malfunctions in body. Damgaard et al. 2006 [1] and Lu et al. 2015 [2] have explained the different pesticides accumulation in human milk due to pesticide residues on food. Nicolopoulou et al. 2016 [3] described the harmful effects of different chemical pesticides, which cause serious health issues and sometimes result in cancers of different body tissues/organs. Chemical pesticides and other harmful chemicals are accumulated in the environment and when animals, insects or other birds eat contaminated food or breath in the polluted air, they are at risk of metabolic dysfunctions and even cause death [4].

The farmers behavior in application of harmful chemical pesticides is very important because they should manage the use of pesticides at different levels and should not apply pesticides at or near the time of harvest [1]. Pesticides cause serious human chronic diseases such as different types of cancers, diabetes, neurodegenerative disorders like Parkinson, Alzheimer, and Amyotrophic Lateral Sclerosis (ALS), birth defects, and reproductive disorders [5]. Concern about the environmental impact of repeated pesticide use has prompted research into the environmental fate of these agents, which can move from treated fields to air, other land, and water bodies [6]. The pesticides application to plants does not remain only to plants or target insects, but they accumulate in the widespread ecosystems such as aquatic ecosystem, aerial ecosystem and terrestrial ecosystems [7], [8], [9]. The biodiversity is deteriorated in landscapes of agricultural areas and a dramatic loss to biodiversity is seen publicly [10].

Recently it has been reported that more than 70% of insect biomass has been decreased since last few decades in Germany and a notable decline in birds and insect populations is also observed [11]. To some extent, biopesticides are also harmful to human health, environment, animals, birds and most importantly the insects which are necessary for plant pollination, but they are not as harmful as chemical pesticides [12].

History of biopesticides

Historically plant derived extracts were used in 17th century when nicotine was used as control agent against plum beetle. Agostine Bassi in (1835) [13] revealed that white muscadine fungus (*Beauveria bassiana*) can be used against silkworm which cause infectious disease in it. The use of biopesticides formulations in eco-friendly manner is not a new as these technologies have been used in various forms since human civilizations. Use of mineral oil as plant protectants was also reported in 19th century. The first biocontrol *Bacillus thuringiensis* was isolated from diseased silkworm by a Japanese biologist Shigetane Ishiwata in 1901. Ten years later in 1911 a German scientist Ernst Berliner rediscovered it from diseased caterpillar of flour moth. In 1920 French's started *Bacillus thuringiensis* (Bt.) as biocontrol agent and in 1938 Sporeine was the first (Bt), which was available commercially [14].

Out of total world, China feeds 22 % of population with only 7 % planet's arable land. In China land is profoundly and recurrently used for agriculture even in traffic triangles, road embankments, walls and balconies of buildings. In comparison of land with other countries like Saudi Arabia 1%, India 50%, U.S 20% and France 32% China has only 10-15 % good agriculture land. Traditionally, China has emphasized on high production to feed large population, but climatic factors, wars and politics mitigated good intentions. (Agriculture in China; Library of Congress report 1980s icweb2.loc.gov; accessed in January 2013). People's Republic of China produced 3.741 million tons and sold out 3.495 million tons of chemicals pesticides in 2021. However, output of pesticides production (herbicides, insecticides and bactericides) has decreased as compared to recent years.

According to United States Environmental Protection Agency (USEPA) biopesticides are those pesticides which are derived from natural resources such as animals, plants, bacteria and microbes (Fungi, Virus and nematodes). According to European Union (EU) it is a type of pesticides based on microorganism or natural products [15]. Biopesticides is combination of two words Bio means life/living and pesticide to kill pests (harmful insects, weeds and diseases). Mainly biopesticides are derived from living organism including different plants having phytochemicals activity, minerals, and microorganism including bacteria, fungi, virus and nematodes [16]. Biopesticides and their by-products (semiochemicals) are mainly used for the management of harmful pests of crops [17], [18].

Classes of biopesticides

The Environmental Protection Agency EPA divides biopesticides into three main categories on the basis of active ingredient like; Biochemical, Microbial and Plant incorporated protectants [19]. EPA sorted biopesticides as those acquired from living organisms and more than hundreds of pesticides product are enlisted (environmental protection agency EPA 2013) [20]. Kachhawa D [21] has described different classes of biopesticides produced by microorganisms based on source such as virus, bacteria, fungi, protozoa and nematodes. Biochemically active pesticides are naturally extracted or synthesized are similar in structure and function to naturally occurring resources and distinguished from synthetic pesticides on the basis of structure and mechanism of action by which they kill target organism. The European pesticides regulation (EC) has recommended the use of biopesticides as alternative source of chemical pesticides but also recommended even less use of biopesticides for production of organic food [22]. Biopesticides are effective tool for Integrated Pest Management (IPM), long term and environment friendly approach for pest management [23].
Internationally biopesticides promoting organizations like International Biocontrol Manufacturer's Association (IBMA) and the International Organization for Biological Control (IOBC 2008) used the term 'biocontrol agents' (BCAs) instead of biopesticides. International Organization for Biological Control divided BCAs into four main groups microbial biocontrol agents (41%), microbial bio-control agents (33%), naturally occurring products (26%) and semiochemicals [16].

Biochemical pesticides

These are naturally occurring nontoxic substances such as plant extracts, fatty acids and pheromones that manipulate with mating i.e., insect growth regulator (IGRs) sex pheromones which are extracted from aromatic plants to repel and attract to kill insects. EPA has constituted a particular committee to make criteria for the classification of different extracted substances as biochemical pesticides

Botanical pesticides

Control of insect pest by natural compounds was used in the ancient time and in 19th century these natural compounds were established on scientific basis and widely used in 20th century. Plants naturally adopt offensive or defensive system from being damaged by other predators such as some plants have developed toxic compounds which are highly harmful for insects [24]. Out of plant extracted products tar and vinegar are used as pesticides and biocides for wood preservative and use of this technique of wood vinegar increased rapidly in Asian countries including China, Japan, India and Thailand. Due to energetic development of biopesticides, numerous botanical pesticides have got active place in the market since the last decade [24].
Among botanical pesticides neem has been historical used against household and pests of stored products. Neem's application as insecticide was attained by (Pradhan) [25] who successfully protected crops by application of neem even at low concentration 0.1 % kernel suspension. Due to insecticidal potential of neem leaves, seed and their selectivity, it can be recommended for management of different crop pests [26]. Azadiractin contains strong anti-feedants and insect growth regulator activity and also affects physiological activity of insects [27]. The effectiveness of neem products against mosquitoes was demonstrated [28]. *Melia azedarach* is deciduous plant also known as Chinaberry or Persian lilac tree having insecticidal properties in fruits and leaves and it has been used against several insects. *M. azedarach* is used as insecticide which is effective for growth retardation, fecundity reduction, molting disarray and behavioral changes [29]. It was reported by Isman [30] that more research work is in progress regarding publication numbers on botanical pesticides especially in China, India and Brazil, but the ratio of application value is less. Kumari et al. [31] reported that more than 6000 plant species have been screened out against several types of pests and about 1005 plant species have phytochemicals activity, 384 with antifeedants, 297 with repellent, 27 with attractants and almost 31 with growth inhibiting properties.

Pheromones

These are chemicals produced by insect to stimulate behavioral reaction among individual of same species, there may be sex pheromones, aggregation pheromones, or alarm pheromones. Pheromones have become efficient tool for monitoring and management of pest population and presently more than 1600 pheromones and attractants have been reported [32]. The utilization of pheromones is advantageous in agriculture as easy monitoring pest, lower cost, host specificity and easy to use [32]. US EPA has registered 30 product based on mating disruption pheromones as biological agents against lepidopteron pest [33].

Microbial pesticides

From the beginning of 1980's to date different approaches are employed for the acceptance of biopesticides market and approach to farmers. Microbial pesticides comprise of microorganisms as active ingredients (fungus, bacterium, virus, nematodes and protozoan or algae). Microbial pesticides control various types of harmful pests and different active ingredients are specific for different kinds of target pests i.e., some fungi control weeds while other can control specific insects. The extensively used microbial pesticides are bacterium based strains of *Bacillus thuringiensis*, (Bt.) that can effectively control pest of vegetables and other field crops [34]. Bt produce mixture of different proteins which kill one or more related species of insects mostly at larval stages. Rajput et al. 2020 [34] reported that some Bt. active ingredients such as *Bacillus thuringiensis israelensis* (Bti) and *Bacillus sphaericus* 2362 (Bs) are toxic for dipterous house hold insect like flies and mosquitoes. Among microbial pesticides, establishment of Bt. gained commercial rank from the last four decades [34]. Commonly available Bt. based formulations are the combinations of dried spores and crystalline toxins that are applied on plant or others desired location to kill insect.

Different species and sub-species of bacteria are recommended and accepted as biopesticides against insects and diseases. These species include *Bacillus thuringiensis kurslaki* and *aizawai* having highest controlling ability mainly against larval stages of Lepidopterist insect. *Bacillus thuringiensis tenebrionis* is effective against Colorado potato beetle both at larval and adult stage of coleopterons. *Bacillus thuringiensis japonensis* strains are effective control tool for soil inhibiting beetle [35]. These products produce proteins that bind to insect gut receptors and ultimately kill the target pest [36]. Bt. is marketed worldwide and used mainly against Caterpillar, Mosquito larvae and black flies. Other strains of bacteria like *Agrobacterium radiobacter*, *Pantoea agglomerans* strain E 325, *Agrobacterium tumifaciens*, *Streptomyces lydicuses* strains WYEC 108 are used for new biopesticides formulations such as Actinovate SP, Contains WG are proving as advantageous in field conditions in USA [37]. *Agrobacterium radiator* strain K84 is a bacterium found in roots area of several plants and in soil which is a good biocontrol agent used against crown gall disease under nursery and greenhouse conditions.

Fungi

Among microbial pesticides several fungal derivatives are also a key source of pest control, an important example is *Metarhizium anispoliae* and hyphomycetes entomopathogenic fungi comprising of several strains of different hosts which are widely used for the control of insect pests [38]. Fungal derivatives are used against surface insects and soil born pathogens is *Trichoderma harzianum*, *Rhyzoctonia*, *Pythium* and *Fusarium* [39]. *Metarhizium anispoliae* are also important pharmaceutically and used as control agent for malarial vector species. They are also applied as a tool for research and development sector [40]. Entomopathogenic fungi (Hypocreales) were used in potato against potato chip diseased prevalent area and also for the control of potato psyllid *Bactericera cockerelli* (Sulc) [41]. It was reported by Domsch et al. 1980 [42] that *M. anispoliae* has been accepted as safe agent against pests, environmental friendly and good alternative of conventional pesticides. Currently such entomopathogenic fungi are under development for production on commercial basis [43]. Faria et al. [44] reported that *M. anispoliae* have been used on large scale in different countries of the world like Brazil, where 100,000 ha of sugarcane crop was treated for the purpose of pest control.

Viruses

These are the derivative of several viruses used as microbial pest control. Different formulations are available for pest control at larval/caterpillar stages of insects. Granulosis Virus (GV) is an effective control agent against oriental fruit moth and also a proficient tool for management of codling moth (*Cydia pomonella)* a serious pest of apple [45]. For insect pest management more than 24 different *baculovirus* species are registered [46]. It was reported by Lepointe et al. [40] that out of all using microbial pesticides the total market share of baculoviruses is 6% and baculoviruses are applied on millions of hectares against variety of insect over the years [40]. However, after use of baculovirus for many years against pest problem no adverse effect has been attributed.

Nematodes

Entomopathogenic nematodes are hot products in current biopesticides market. These are used in plant protection against different kinds of pests. In early 1990 Copping et al. [47] discovered two effective entomopathogenic nematodes used against insect from two different kinds of genera *Steinernema* and *Heterorhabditis*. However, a little is known in relation to availability of indigenous nematodes to manipulate population of insect pests. Nematodes genera *Steinernema* and *Herorhabditis* (Rhabditida) are used as biological control agents in the domain of plant protection [48]. Entomopathogenic nematodes together with symbiotic bacteria like *Photorhabdus* and *Xenorhabdus* can effectively control Coleoptera, Diptera and Lepidoptera pests [49].

Protozoa

Entomopathogenic protozoa are generally host specific, slow acting with complex biological activity. They recurrently produce common chronic infection and infectious spores in several susceptible insect species. *Nosema* species is an important example of most commonly used protozoan derivatives. They are persistent in insect and effect reproduction and fitness of insect. Commonly used protozoans as microbial control agent is moderately successful [50]. *Nosema locustae* is a pathogenic species used against grasshopper [51]. Al-Sadi et al. [52], in 2013 described that *Nosema bombycis*is microsporidium pathogen of Silkworm pebrine, persisted during mid of 19th century in Europe, North America and Asia. It was reported by Fu 2016 [53] that pebrine still causes loss to economic level in silk producing countries like China.

Plant Incorporated-Protectants (PIPs)

Plant incorporated protectants are pesticidal substances produced by plants containing already added genetic material. By this way when plants are genetically modified, their metabolites are regulated by Environmental Protection Agency EPA and termed as pesticides. PIPs are safe for the environment but to some extent they cause lowering of food quality because of built-in modification of plant metabolites [54]. However, these PIPs are not effective against pathogens because with the passage of time the resistance is evolved in pathogens against specific modified metabolite/PIPs [55]. Among biopesticides (biochemical and microbial) PIPs are classified as safer and better alternatives of synthetic chemicals. Registration of PIPs was started in 1995 and federal standards were updated, and laws passed down for production and registration of these products. C5 Honey Sweet Plum (C5) is an example of PIPs which is used against stone fruits and almond pest, Plum Pox Virus (PPV) some other diseases like a.k.a. Sharka disease, *Bacillus thuringiensis* Cry1A.105 and Cry2Ab2 used against lepidopteron pest in soybeans [56]. Although plant incorporated protectants are beneficial for pest control, but they have some side effects such as their metabolites, when accumulate in fruits, leaves, stems etc. they become harmful for human as well as animal health.

Current status of biopesticides

People's Republic of China is leading country in the world in research and development (R&D) of biopesticides, but lack of awareness is big hurdle among Chinese farmers for adoption of biopesticides which leads them to use dangerous pesticides in wrong way. For the China's plan of zero growth of pesticides consumption till 2025, more efforts are required to reduce the use of chemical pesticides and development of more biopesticides for sustainable agriculture. This issue was widely mentioned in catalogue of key products and services in strategic engineering industry (2016). Similarly, issue was published by National Development and Reforms Commission of People's Republic of China and investigated eight industries which are concentrating on biopesticides on priority basis.

China has recently claimed first rank among global production and development of biopesticides market. According to Customer Communication Management (CCM) research, China has developed complete system of biopesticides (microbial, botanical, agricultural antibiotics and biological pest control). With the forecast of CAGR 18.5% target was set for volume consumption and 19.4% value demand for 2025 for analysis period of biopesticides market. Currently more than 90% of active ingredient of biopesticides have been registered which accounts for about 11-13 % of total registered pesticides. Due to high-cost ratio of biopesticides to synthetic pesticides farmers feel hesitation in using of biopesticides.

In China commercialization of potential product is the main problem in biopesticides development, however theoretically approved potential products can find way from lab to real development, like other countries which launch research into market. Hence despite of weak commercialization registration of biopesticides increasing continuously especially in the form of registration of microbial pesticides. (**Fig. 1**) shows the number of registered biopesticides among which most 3575 are biological pest control and lowest are 4 which are agricultural antibiotics (Institute for the control of Agrochemical, Ministry of Agriculture 2020).

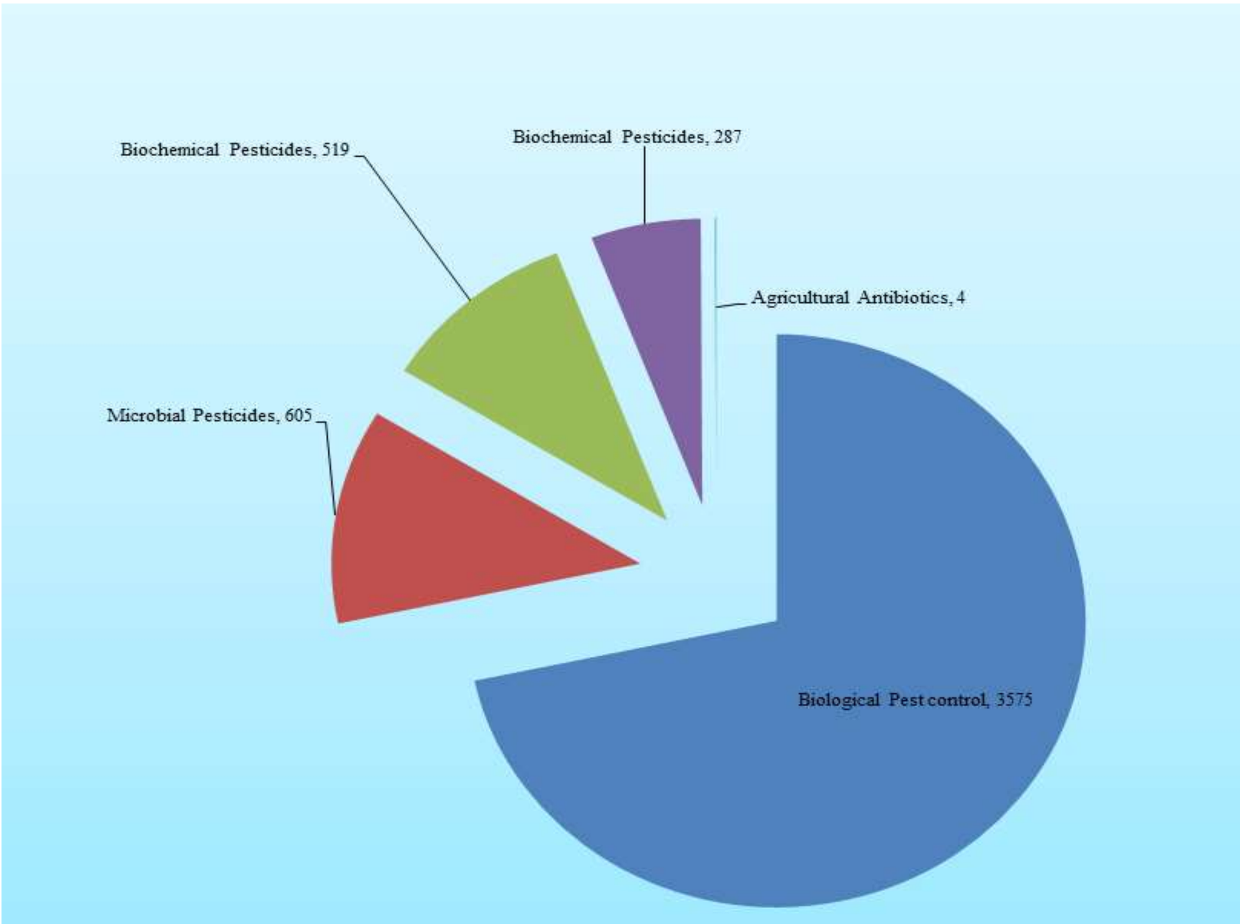

Fig. 1: Registered Biopesticides formulation and field test in China, 2020; Source: Institute for the control of Agrochemicals, Ministry of Agriculture.

Biopesticides development in China

Biopesticides in China refer as botanical pesticides, microbial pesticides, biochemicals, GMO crops, natural enemies and agriculture antibiotics. **Fig. 2** showed no. of biopesticides active ingredients and registered products in China [57]. Different manufacturers are active to fulfill the information gap and reduction of lack of awareness among farming community. According to CCM's research different companies like (Jiangxi new Dragon Biotechnology Co., Ltd and Jiangxi Tianren Ecology Co.) developed a brand-new business pattern "Biopesticides+agriculture activation service" which meets Chinese farmer's demands and shows plentiful profit for farmers. In the meanwhile, Chinese govt. has implemented different polices for the promotion and development of biopesticides business to put forward the expansion of subsidized program of less toxicity of biopesticides. Currently by the interest and increasing effort of Chinese govt. and manufacturers, Chinese pesticides industry is expecting great use of potential biopesticides soon and offering opportunities for foreign sellers and investors to get a piece of cake from growing market of China. **Fig. 3 & 4** showed China biopesticides export and major destinations respectively. Some of the commonly registered biopesticides in China are given in the (**Table 1**). Some of the mostly sold biopesticides are given in (**Table 2**).

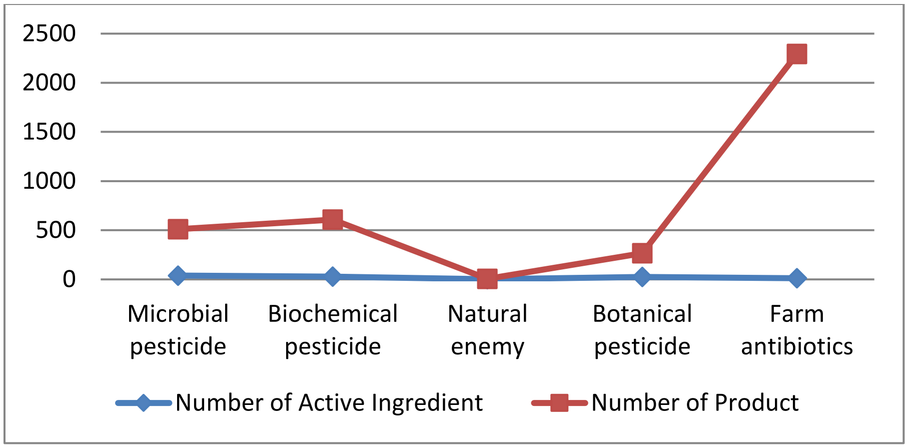

Fig. 2: China's Biopesticides Registration Status 2019 (active ingredients)

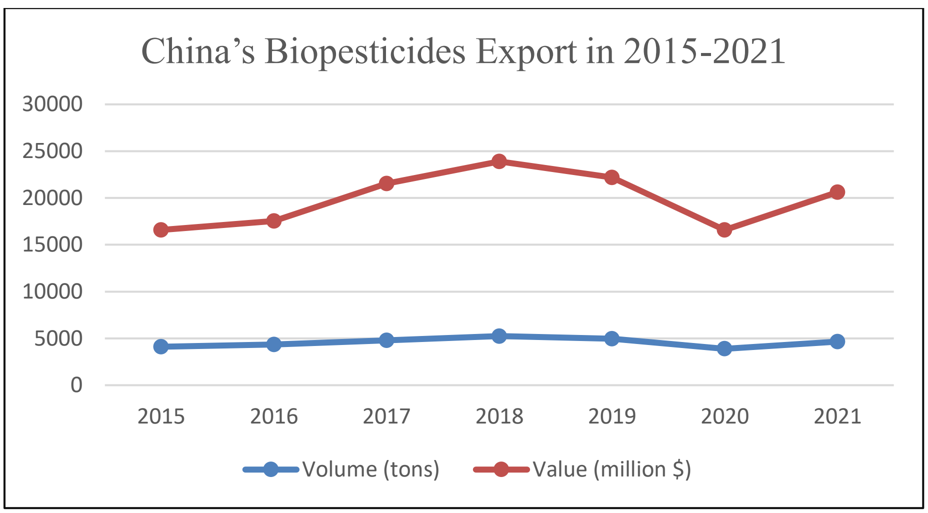

Fig. 3: China's Biopesticides Export in 2015-2021

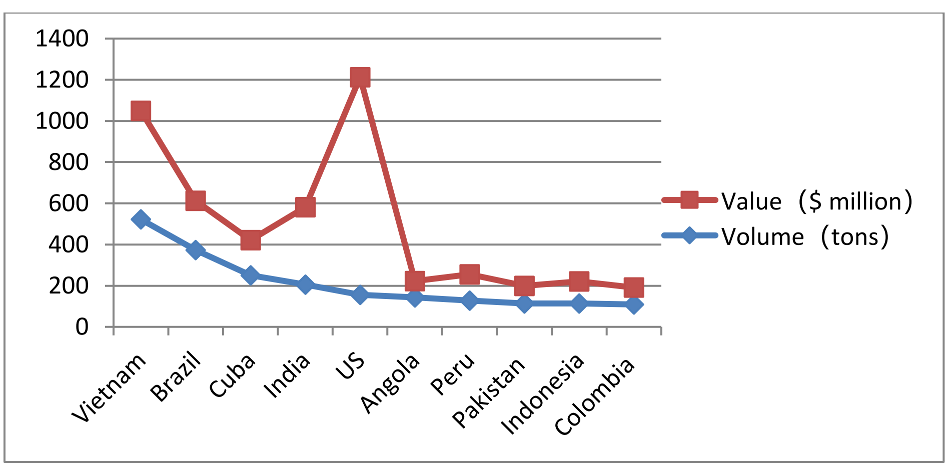

Fig. 4: Top 10 Destinations of China's Biopesticides Export in 2020

Table 1: Commercially registered biopesticides in China

Sr. #	Biopesticides categories	Target pest
A	Bactericides	
1	*Agrobacterium radiobacter*	Crown gall
2	*Bacillus sphaericus*	Crown gall
3	*Bacillus polymyxa*	Crown gall
B	**Fungicides**	
4	*B. cereus*	Bacterial wilt, sheath blight/rice false smut, bacterial wilt
5	*B. licheniformis*	Downy mildew, *Fusarium* wilt
6	*B. subtilis*	Bacterial wilt, root rot, tobacco black shank, rice blast, rice false smut
7	*Trichoderma* spp.	Fungus downy mildew, *Rhizoctonia cerealis* , gray mold
C	**Fungicides & Bactericides**	
8	*P. fluorescens*	Bacterial wilt, root rot
D	**Insecticides**	
9	*Bacillus thuringiensis* subsp. Aizawa	Lepidopteran pests
10	*Bacillus thuringiensis* subsp. Israelensis	Lepidopteran pests
11	*Bacillus thuringiensis* subsp. Kurstaki	Lepidopteran pests
12	*Pseudomonas alcaligenes*	Locusts, grasshoppers
13	*Beauveria bassiana*	*Monochamus alternatus*, *Dendrolimus Punctatus*
14	*Conidobolus thromboides*	Aphids
15	*M. anispoliae*	Cockroaches, grasshoppers, locusts
16	*P. lilacinus*	Nematodes
17	*Pochonia chlamydosporia*	Nematodes
18	*Dendrolimus cytoplasmic* polyhedrosisvirus	Virus Caterpillars
19	NPV, *Ectropis obliqua hypulina* NPV, *Laphygma exigua* NPV, *Prodenialitura* NPV, *Buzura suppressaria* NPV,*Gynaephora ruoergensis* NPV,*Mythimna separata* NPV	Virus Beet armyworm, lepidoptera, looper, *H. armigera* , *Laphygma exigua*
20	*Periplaneta fuliginosa* densovirusvirus	Cockroaches
21	*Pieris rapae* GV, *Mythimna separata* GV, *Plutella xylostella* GV	*Pieris rapae* , *Plutella xylostella*

Source: [56] and [46]

Table 2: Mostly sold biopesticides

Sr. #	Biopesticides categories	Target pest
1	Validamycin	Fungi
2	Tricyclazole	Fungi
3	Oligosacharins	Fungi
4	Kasugamycin	Bacteria, Fungi

Source: China Crop Protection Industrial Association (CCPIA), Consumer Communication Management, CCM Data and Business Intelligence, 2019.

Future Prospects

Currently there are about 260 biopesticides enterprises in China, which account for 10% of total pesticides production. Annual output of biopesticides formulations is approximately 14000 tons which account for 11% of pesticides output and value respectively. At present China is growing rapidly regarding biopesticides development and new biopesticides formulations are emerging such as Ningnanmycin, Shenqinmycin, Atailing etc. (China Pesticides Registration Watch 2020) [59]. Biopesticides are always a better alternative to chemical pesticide which are harmful to the environment as well as human health and other organism's lives [60].

At the end of 2020 a total number of 35600 pesticides formulations were registered in China covering 670 active ingredients as well as 3575 biopesticides formulations covering 105 types of active ingredients. China biopesticides registration is still concentrating on antibiotic represented by Abamectin and up to the end of 2020, 2379 agriculture antibiotic products were registered, which accounts for 64% of total biopesticides registration. As replacement of synthetic pesticides, biopesticides are receiving more attention of government and public sector in China.

Currently a new bio-fungicides namely Timorex has been registered from Ministry of Agriculture People Republic of China for the control of powdery mildew of strawberry and early blight of potato [61]. New formulations and discovery of new pesticides is required for safer food production which will help us in new era food security [62]. To reduce the consumption and harmful effects new pesticides which are least toxic and having effective control are being issued in 2020 by action program of zero growth of pesticides utilization to 2025 by Chinese Ministry of Agriculture to maintain estimated chemical pesticides production by APIs 3.768 million tons and sale 3.628 million tons respectively [63].

Conclusion

Continuous supply of food stuff leads agriculture system to be strongly depending on fertilizers and pesticides. For producing more food farming community using more chemical pesticides lead generations to blind future. In current situation biopesticides are emerging as suitable alternative of synthetic pesticides which needs to strengthen green alternatives by pushing red poisonous chemicals to save ecosystem and human beings. This review article gives an explanation about different classes of biopesticides, their importance in production of healthy food safe from pathogens and chemical pesticides as well as current status and production of these biopesticides from different sources universally and in China too. Increasing demand of organic food can also be fulfilled by promoting biopesticides. However more research and development of biopesticides are required for safe food grain production in China.

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Authors contribution

M A and A J, designed this study theme, collected data and drafted manuscript; A R S, S U and A S worked on graphics and figures; T u H, Z N and F A reviewed & improved the entire article; Z A & SQR improved English language of article; and J M supervised, intellectually supported & provided APC.

Conflict of interest

The authors declare no conflict of interest.

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