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Review Article

The Need for Pest Control and the Possibilities of Pesticide Development in Accordance with the Requirements of Safe Food Production

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Abstract

The scientific and technical development that made the industrial revolution possible not only transformed the social structure worldwide, but also imposed new requirements on food production and necessitated changes in plant cultivation procedures. Within this, pest control management underwent a radical change in the last century, and the use of pesticides (synthetic chemicals) became widespread. The main reason for this is the maintenance of the profitability of the production by guaranteeing the reliability of the harvest. This latter aspect usually is not taken into the account by those who oppose the use of pesticides. In the past half century, the pesticide assortment has undergone significant changes, currently around 2000 different active ingredients are available, among which the proportion of synthetic super selective molecules has increased. Although this contributed to the reduction of concerns about their use, the widespread application of these mono site inhibitors imposed new requirements. On the one hand due to the acquired resistance against them within the pest population, and on the other hand due to the appearance of new, previously insignificant pest species. Among them, the phytopathogenic bacteria are of increasing importance: we currently do not have a sufficiently effective preparation that can be used to control them widely in plant cultivation. There is an urgent need to develop pesticides suitable for combating newly emerging diseases.

In this paper, the author examined this question from the inventor's point of view, sharing the experiences of six decades of research in this area.

Antecendents

The millennia-long history of plant cultivation is also the history of *protection against factors that threaten* crops. The tools used (Figure 1) varied from age to age, depending on the current technical development of the given society, but they were usually the most effective tools available. Nowadays, the use of various chemicals is the most effective plant protection method. However, it is necessary to underline that the tools used in plant protection are not applied to increase the amount of the yield, but to increase the safety of the harvest.

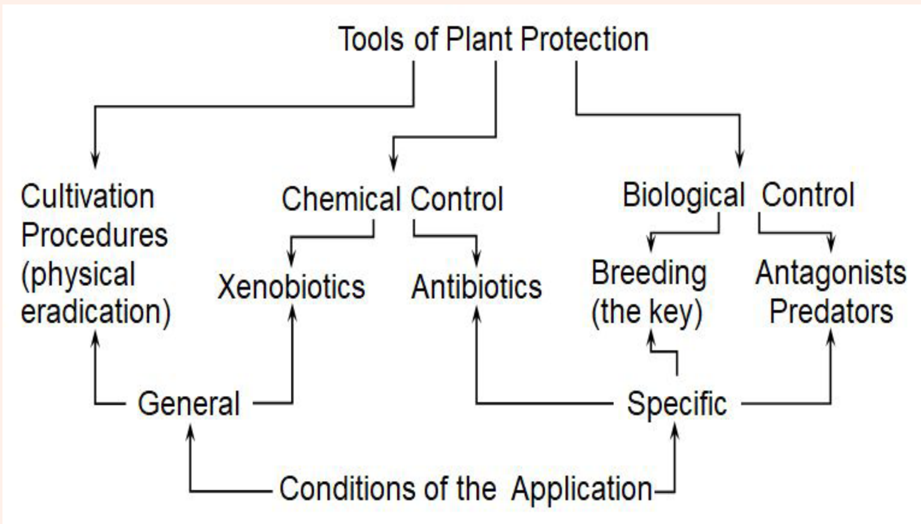

Figure 1: Recently used pest management practices in plant protection and their relationships.

The goal is not to eradicate living organisms, but to reduce the activity of pests to a level that is negligible from an economic point of view. So, the pest management is a set of procedures to guarantee crop safety. The widespread use of synthetic chemicals (xenobiotics) is a consequence of the technical/scientific development of the last century and the transformation of the social structure (Figure 2).

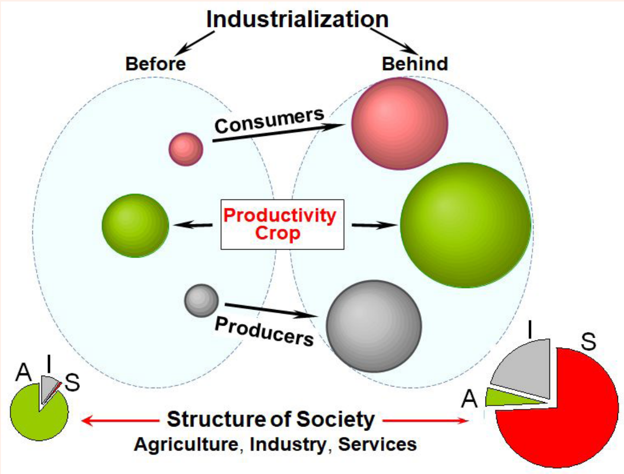

Figure 2: The effect of industrialization on changes in the social structure, needs and available possibilities in the last century.

Source: Imported of Oros, 2004 [1]

Note: The area of the circles and sectors in the figure is proportional to the indicated parameter; A=agriculture, I=industry, S=services (non-goods producing sectors). The area delimited by a dashed line shows the limited space available.

Phytopharmacology, a new branch of science that is emerging today, deals with the development of chemicals that can be used to eliminate biological factors that threaten the effectiveness of plant cultivation, as well as the scientific basis of their use. The way of approaching and solving the tasks facing phytopharmacology is in general aspects similar to that used in medicine, however, due to the different areas of use, the methods developed there cannot be used directly. Three very important differences should be mentioned:

I. The risk of using chemicals is qualitatively different in human medicine than in plant protection (Table 1).

II. The range of organism to be protected differs significantly. While human pharmacology serves the protection of one organism, the human being, the subject of phytopharmacology is the protection of hundreds of organisms that are significantly different from a taxonomic point of view.

III. There is no similar immune system in plants, which is extremely important in the defense of human body (vertebrates).

Present art of technology

The use of plant protection products in developed industrial states is currently extremely extensive, and their importance continues to grow proportionally as backward regions catch up (Figure 3). All this even though today some environmental protection groups in big cities - without adequate professional information - consider pesticides to be among the number one sources of danger to human life, and often exert strong political pressure to limit or completely ban their use. However, it is obvious to experts that crop protection is insoluble without the use of chemicals, and the question is not whether to use these chemicals, but what, for what purpose, where and when. The directions that can be observed in the development of plant protection products are partly determined by scientific results and economic needs, and partly by social/political requirements. Even though the first plant protection product in today's sense was developed against pathogenic fungi (Bordeaux juice/grape downy mildew: Millardet and Gayon, 1885 [2]), and at first the developments were mostly in the field of insecticides, nowadays the greatest diversity has been achieved in relation to herbicides. To a large extent, there are social and market reasons for this, because due to the development of large-scale industry, the number of people taking up jobs in agriculture has decreased, and the necessary workforce is no longer available to carry out one of the most labor-intensive tasks (weeding) (Figure 3).

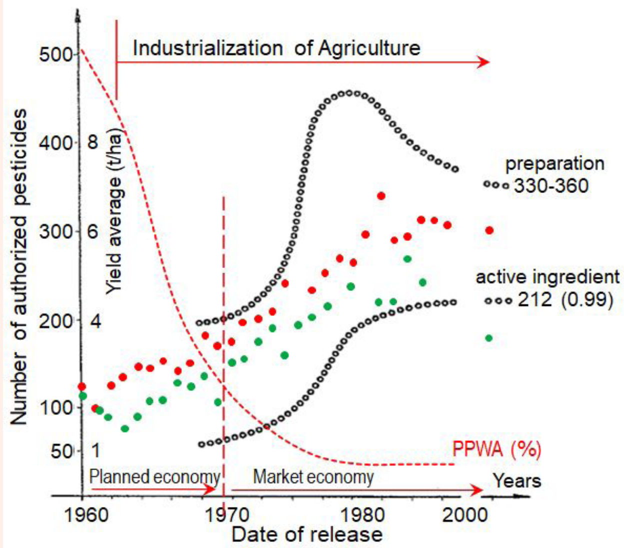

Figure 3: Changes in the number of active substances and preparations used in Hungarian agriculture as a result of the reorganization of the method of plant cultivation.

Source: Data imported of the Yearbook of Hungarian Central Statistical Office

Note: PPWA = Proportion of population working in agriculture, decreasing of 52 to 4 percent. Instead of a centrally managed planned economy, the reform of economic management placed agriculture on a market basis.

The yield averages of wheat and maize were marked with red and green spots. Clearly seen that the industrialization *per se* did not improved the efficiency of production, however, allowing free competition led to a trifold increase in efficiency of production as well as to essential diversification of pest management practices.

As we can see in Figure 2, the increased human workforce does not work in agriculture, but the needs of the increased consumer mass must be met by agriculture. With regard to the increase in productivity and the mass of crops, three key factors that appeared in recent times should be highlighted: mechanization, introduction of chemical, and breeding processes. The scientific basis for the latter was and will continue to be provided by the results of chemistry and comparative (agro)biology. The development and technological changes were extremely rapid (Figure 3). The number of preparations to be used is primarily determined by the diversity of crop production in the given area. Because the scope (spectrum of effects) of any compound includes a finite number of organisms, the specific efficiency (selectivity) projected onto organisms is a basic requirement (Table 1).

Table 1: The most important relationships to be evaluated for development and application of pest control agents.

Exposed organisms			Therapeutic index[a]	Persistence (days)
To be controlled	Age	To be protected (P)		
Pest (C)	Traditional	*Homo sapiens*	no harm	not
		Host plant	>5	1-30
		Vertebrates	>100	not
		Bees	>100	not
		Saccharomyces spp.	>3	not
	Future	Symbionts	>10	not
		Antagonists	?	not
		Predators	?	not
		Ecosystems	?	?

Legend: [a]Therapeutic Index (T.I.) = MTD_P/MID_C, where MTD and MID are maximum tolerated and minimum inhibitory doses of control agent, respectively.

The mass of the active ingredient to be used per unit area has decreased by about twenty in a hundred years. Currently, the amount to be applied is about 1-10 g of the most effective compounds per hectare. In addition, the therapeutic value also increased, the selectivity of the preparations increased, i.e., the strength of their side effects decreased. In this regard, the most important is the warm-blooded toxicity, from which it is highly probable that human toxicity can also be inferred, and in this field very significant progress has been achieved (Figure 4). In the last four decades, the acute warm blood toxicity of active substances (measured in rats) has decreased to a fraction of what it was before, from an average of 50-200 mg/kg to 2500-15000 mg/kg. This raised a new, previously neglected issue, the side effect of poisons presents in highly sublethal doses and shed new light on Paracelsus' "*Poison in large quantities, medicine in small quantities.*"

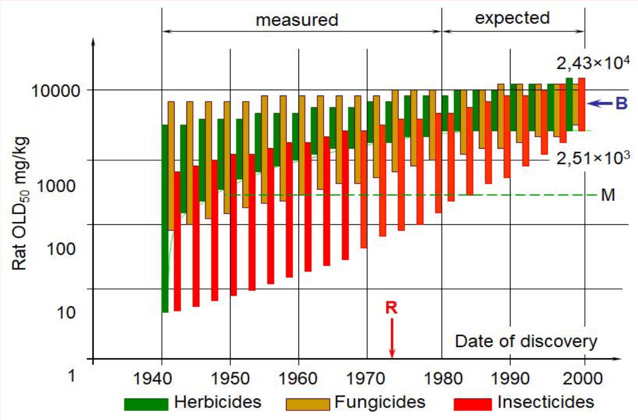

Figure 4: Changes in mammalian toxicity of pesticides

Source: Imported of Oros, 1993 [3].
Note: The trends were calculated from data obtained between 1940 and 1980, columns betwen the envelope second order polynomial functions mark the range between least and most toxic substances ($p<0.05$).
Abbreviations: R – Emergence of acquired tolerance to carbendazim, M – the requested maximum toxicity for new discoveries, B – the toxicity of KF73 approached by means of Sun's model [4]. (This preparation contain mixture of carbendazim and furoxone at 7 to 3 weight ratio (Ángyán et al., 1985 [5])

This brief historical overview is justified even if we want to talk about the future. Because progress has not made the toolbox for solving current tasks obsolete, the new methodological results fit organically with the old ones, expanding their possibilities. For example, traditional methods of resistance breeding are not replaced by biotechnology but made more efficient. However, the importance of side effects has grown not only in human aspects. It has also become important to study the effects on non-target organisms that are treated and, in some cases, located in more distant areas (Table 1). The results of these tests can serve as a basis for the development of new active ingredients. In the near future, a strong increase in the demand for preparations that can be used against prokaryotic plant pathogens can be expected. There are two main reasons for this:

I. There is not a single synthetic bactericide that can be widely used in the current range of active ingredients (Figure 5).

II. More than a hundred compounds, including extremely effective compounds, are available for treatments to prevent damage caused by fungi, and because of this, the importance among the bacteria causing root rot is expected to increase.

Traditional fungicides have the most significant bactericidal effect, but only a few of them approach the effectiveness of natural antibiotics in this aspect. The more recently developed ones are highly selective mono site inhibitors not inhibiting bacteria. Modern herbicides and insecticides also protect bacteria. Therefore, the development works can be said to be successful in terms of increasing the selectivity of the effect, however, this situation imposed new requirements.

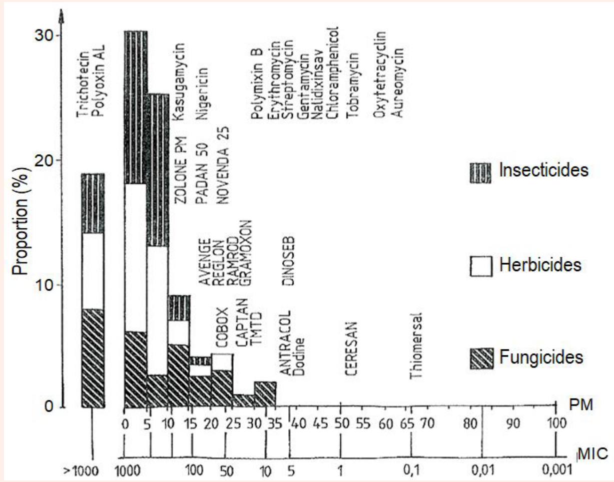

Figure 5: Classification of plant protection products marketed in Hungary as bactericides according to the degree of their effect.

Source: Imported of Oros, 1993 [3].
Note: The abscissa shows the efficiency classes (HM= efficiency index, MIC= lowest effective concentration or minimum inhibitory concentration), while the size of each class (as a percentage of all tested cases; 25 species vs 204 pesticides) is shown on the ordinate, according to target groups. In the row above the insecticides, the antibiotics widely used in 1980 are listed in the order of their effectiveness against plant pathogenic bacteria.

Table 2: Variations of the selective effect measured in relation to plant species and microbes.

Effect	Character	
Area	**Spares**	**Inhibits**
One species	chloroszulfuron → wheat thiomersal → *P. fluorescens*	Flamprop-i → wild oat Diethofencarb → BR fungi
All species	manure	Glyphosate
Legend: BR = Inhibits only strains acquired tolerance to benomyl.		

We speak of a high degree of selectivity when only one organism in the given biocoenosis stands out in terms of sensitivity to the active substance. This naturally ranges between two extremes (Table 2). Examining side effects can also provide useful lessons. As can be clearly seen in Figure 6, the individual bacterial strains form genus-level groups if we classify them according to their pesticide sensitivity. It is clear from this that it is possible to develop a selective bactericide at the genus level.

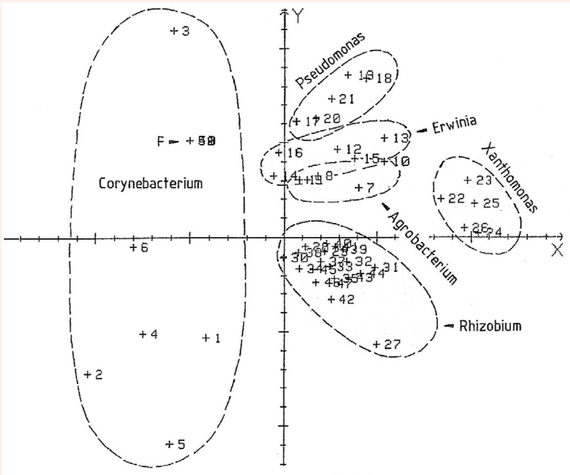

Figure 6: Classification of bacterial strains based on their sensitivity to pesticides.

Source: Imported of Oros, 1993 [3].
Note: The figure was created using sensitivity (MIC) data for 57 pesticides proposed or approved for use in pest management of legumes.

It cannot be decided now what level of selectivity a bactericidal product should possess. However, it seems certain that the effect of an agrobactericide cannot extend to the microbes that accompany humans (*Staphylococcus*, *Streptococcus*, *Escherichia*, *Bacteriodes*, etc.).

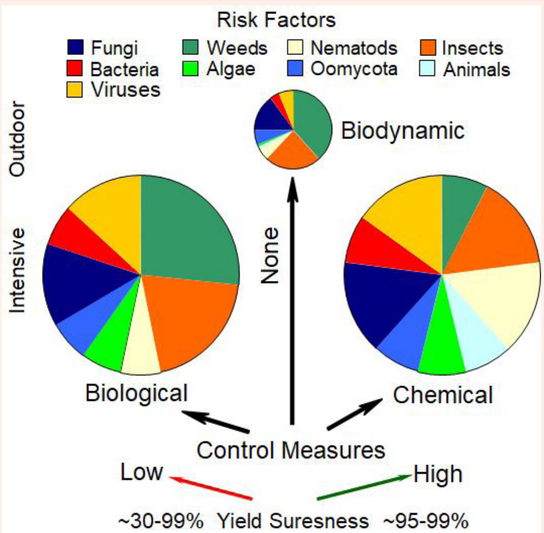

Figure 7: Effect of control methods on risk factors and yield.

Source: Imported of Oros, 2004 [1].
Note: The area of the circles is proportional to the specific amount of the crop, while the size of the slices to the degree of risk.

There are two options for growing crops. One is the passive, minimal intervention (natural) cultivation, the other is the actively intervening cultivation. According to the two approaches, the amount of potential, specific harvestable crop differs dramatically from each other (Figure 7). For example, the same type of wheat yields 8-12 or 60-80 q/ha depending on weather the field is cultivated passively or actively. Regarding plant protection procedures, the two versions of active interventions, - biological and chemical control, - in the background with other procedures corresponding to the given technological level, lead to approximately the same result regarding the amount of the crop. However, three significant differences remain: i) The expected effectiveness of biological methods, - in contrast to chemical methods, - is contingent (approx. 2:5 and 1:500 failure rate, respectively). Therefore, crop safety does not increase predictably after the technological change. ii) The relationship of the risk factors to each other differs in the case of the two sets of methods. This also applies to after-effects (residues). In this regard, there are no reliable experiences with biological processes, unlike chemical ones. iii) The biological control requires a significantly higher degree of expertise, and the security of cost recovery is also lower than in the case of chemical control. Although in the longer term the two types of solutions will obviously be used in a co-ordinated way in a ratio that cannot be determined at the moment, the importance of chemical defense will continue to increase in the coming decades. That is why it is not indifferent in which direction we carry out developments.

Most of the active substances used today are expected to become outdated within ten years or lose their effectiveness due to acquired resistance occurring in the populations of the target organisms. Among the many reasons in favor of chemical control, economic ones stand out: the use of plant protection agents, especially herbicides, has dramatically reduced the need for human labor, and the productivity of crop cultivation has increased to an extraordinary extent. Chemical weeding is significantly cheaper and more environmentally friendly than mechanical or manual weeding. In addition, unlike pests and pathogens, weeds can continuously compete with cultivated plants throughout the entire vegetation period, while the populations of the other two groups usually cause damage periodically, as if in waves. Among the biological factors that damage the crop, weeds are also given a special meaning by the fact that their ability to compete usually exceeds that of cultivated plants, at least in some stages of the vegetation, and in this regard, breeding has not achieved such outstanding results as in the case of disease resistance. There is no doubt that the most environmentally friendly plant protection method can be considered to be breeding for resistance to dangerous factors. Although the introduction of new, biotechnological methods, - also from this point of view - has opened horizons that cannot be precisely defined yet.

Consumers' often well-founded aversion to foods from genetically engineered sources also inhibits the spread of new technology. Nevertheless, based on the results so far, it seems that chemical weed control will remain indispensable in the coming decades, since gene sources have not yet been discovered that would allow the introduction of traits suitable for the induction of suitable allelopathic effects. The situation is different with insecticides and antimicrobial substances. Gene manipulations for plant protection have wider possibilities in this regard, as newer biotechnological methods also allow gene transfer between higher taxa (e.g., introduction of genes of bacterial origin into cultivated plants). The development of molecular diagnostic methods enhances the rapid analysis of the results of gene transfer, which helps to estimate the effect of the expression of introduced alien genes on the expected change in the phenotype as well as speeds up the selection process necessary in plant breeding (Deepak et al., 2007 [6]). Withal, the cultivation of biotechnologically modified plants raises many unforeseen and underestimated problems (Baksi, 2003 [7]). These include, for example, the accumulation of phytotoxins or other new metabolites, even those from plant protection products, which were not previously present in food, but are present in the genetically engineered plant (Domingo, 2007 [8]), the effects of which compounds on humans, especially at a chronic sublethal level, are not known at all (e.g., glyphosate metabolites, Cuhra, 2015 [9]). New active ingredients are therefore needed, as the number of factors endangering production is large (Table 3).

Table 3: Relevant pathogens causing economic losses in most important cultivated plants.

No.	Host plants [10]	Production [11] ×10⁶ t/year	Pathogens[a]				
			Virus	Prokaryotes [12]		Eukaryotes	
				Mollicutes[b]	Eubacteria	Fungi	Oomycota
1	Maize	823	40	2	13	150	13
2	Wheat	690	144	1	10	106	6
3	Rice	685	2	0	6	40	3
4	Potato	314	40	4	11	43	10
5	Cassava	232	9	2	5	28	5
6	Soya	231	15	2	6	49	7
7	Tomato	182	14	2	7	46	5
8	Banana	116	9	1	9	71	1
9	Batata	110	6	1	4	52	5
10	Apples	87	8	8	4	90	8
11	Grapes	79	23	5	7	14	1
12	Oranges	75	12	3	7	95	16
13	Sorghum	66	3	1	3	38	4
14	Yams	52	2	0	1	4	3
15	Cotton	25	8	3	3	47	2
		Total	335	35	96	873	86
Number of marketed pesticides[c]			6	1	34	>600	33

Legend: [a]=number known pathogens of crops (APS Disease Compendium); [b]= mycoplasmas and rickettsias, [c]= number of registered synthetic molecules for disease control number of marketed pesticides for the control of pathogens.

It can be particularly interesting to review and rescreening the effect of molecules known or used in other fields according to new aspects. Another possibility of development is to use an optimized mixture of the available active ingredients to increase the therapeutic value, possibly supplemented with different effect enhancers or auxiliary substances. By adding antidotes, adjuvants or synergists, the therapeutic value of several herbicides and insecticides has been significantly increased. For example, one of the "by-products" of the studies is the combined preparation containing carbendazim and furazolidone (Pharmaplant 40 fw), which is equivalent to benomyl and streptomycin against plant pathogenic fungi and bacteria (Table 4). This optimized mixture has special advantages acting against the strains acquired resistance to marketed pesticides.

Table 4: Sensitivity of apple pathogens to pesticides[a]

Pathogen	Disease	KF	Ben.	Str.
E. amylovora W[b]	fire blight	2	>100	2
E. amylovora R[b]	fire blight	1	>100	>100
B. cinerea W[b]	fruit rot	1	0.5	2
B. cinerea R[b]	fruit rot	5	>100	>100
V. inaequalis W[b]	scab	0.2	1	>100
V. inaequalis R[b]	scab	1	>100	Str.

Legend: [a]KF= Carbendazim+Furazolidone (7:3), Benomyl and Streptomycine; Minimum Inhibitory Concentrations were given in mgL^{-1}. [b]Wild (W) and Resistant (R) strains.

Over 2000 active ingredients are currently distributed in world trade, so the possibility of variations like the above seems great. However, this is not determined by the number of available compounds, but by the number of functional groups, which is unfortunately not large. Metabolism is very complex and apparently there are a large number of receptor sites, but the number of sites (reactions) that can be selectively and economically inhibited at least at the species level, - i.e., as a consequence the entire cell function stops, - is limited. In ecosystems, organisms use the compounds produced to paralyze such sites (biogenic antibiotics) to displace competitors, which is why studying the mode of action of various biocides can provide important results for the design of new active substances. In addition to combinations, this is an encouraging option. Biocides are sometimes used on their own (antibiotics: abamectin, kasugamycin, polyoxin, etc.) in plant protection, or their analogons are used (nereistoxin pro-derivatives, strobilurin analogons, etc.). In a similar way, analogons of molecules (hormones, coenzymes) involved in the regulation of metabolism can also be used. For example, the non-protein aminoacid, coronatine, - produced by rhizoplane habiting *Pseudomonas*, - significantly improve the tolerance of host plants to obligate pathogens (Figure 8).

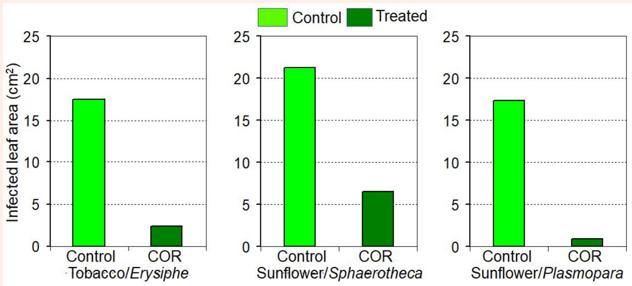

Figure 8: Effect of exogenous amino acid on plant disease resistance.

Source: Imported of Oros et al., 2000 [13]
Note: Control - water, COR - 100 nm coronatine per plant applied *pre infectionem*.

Numerous similar results have been published. These biogenic compounds are extremely effective, and their scope is usually narrow, which is why the public perception considers them "environmentally friendly". However, the market value of such solutions is highly doubtful because they do not remove the pathogen of the phytosphere, so in the event of a change in the factors affecting the disposition of the host plant (weather), and the pathogens can rapidly multiply and cause serious crop loss. Moreover, for the protection of the sites of action inhibited by natural biocides, - precisely because of their key importance, - effective protective mechanisms also developed during the evolution of the pathogens. Thus, in practice, resistance to preparations made from them or their analogons quickly develops in the populations of the target organisms. Due to the limitations by industrial law, the scientific laboratories carry out extensive exploratory tests; biocides of natural origin are important sources of ideas, and the targeted metabolic pathways are diverse. However, it seems that the inhibition of protein synthesis is the most beneficial, and the use of oligopeptides (n=2-6) or their analogons involved in the regulation of metabolism will develop the fastest. There are partly industrial law reasons for this, as the possibility of variations in this range of compounds is exceptionally large, and the molecular structure can be changed relatively easily without jeopardizing the therapeutic value, the knowledge of their chemistry rapidly develops. Peptides can be used in all areas of plant protection. Their special advantage is that most of the products produced during their metabolism are not foreign to the body and can be broken down without limits. The coronatine, used as a weeding or spraying agent in nanomolar mass, effectively increases the resistance of host plants against obligate parasites (Figure 8). Many analogons of amino acids have, usually, a highly selective inhibitory effect. For example, as a histidine antagonist, the carboranyl analogon of phenylalanine has a lethal effect on the cystospores of oomycetes in picomolar amounts (Oros et al., 1999 [14]). The bradykinin derivative, which plays a major role in the development of insects, effectively inhibits *Candida albicans*, which has become resistant to azole derivatives. The analogon of this peptide forms a synergetic mixture with copper ions (Figure 9). For the practical use of peptides, a number of conditions must be carefully studied (the way they are produced in large-scale industry, their stability, storability, application method, absorption, degradation, etc.).

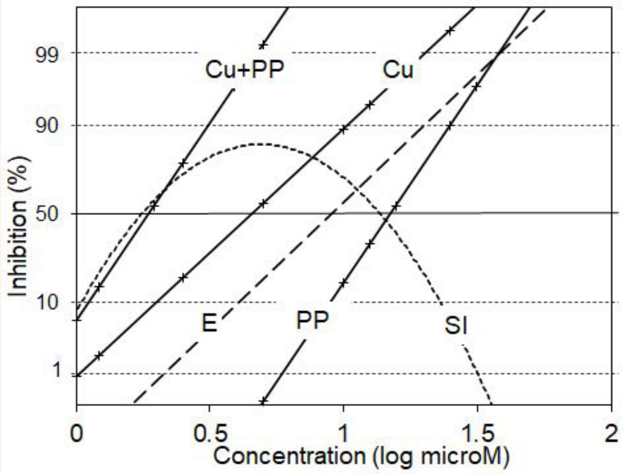

Figure 9: Joint action of copper ions and a penta-peptide against *Plasmopara halstedii* zoosporangia.

Source: Imported of Oros and Nachman, 2003 [15].

Abbreviations: Cu – copper sulfate, PP – pentapeptid, Cu+PP (1:1 mixture). E – The expected additive effect according to Colby (1967 [16]). SI=([C+P]-E) – Dose dependent increase of efficacy of the mixture.

Prospects

The detection of side effects arises as a completely new issue, especially regarding the possible influence of these derivatives on the functioning of master genes. This latter problem may also arise in the case of other biocides of natural origin or their analogons, and so far, little attention has been paid to such aspects. Regrettably, "organic" preparations labeled "naturally derived", "according to public perception", or "in accordance with the generally accepted view" as "harmless" are commercialized without thorough study. The main reason for this is the political activity of the above-mentioned, violent groups that claim to be "environmentalists", and the economic pressure of businesses that support these groups, lurking in the background. In-depth study means not only carrying out the extremely expensive tests required by the licensing authority, but also scientific investigation at the basic research level. As a matter of fact, any fair-thinking person with a medium education in natural sciences can easily see the above; there is a fundamental social interest in ensuring that compounds with either inhibitory or stimulative effects on living beings cannot be placed on the market without scientifically based tests. It is also easy to see that the results of these investigations serve as a basis for further development, not only in the field of phytopharmacology, but in other branches of science as well.

The comparative physiological/biochemical studies, the detection of the mode of action and metabolism at the molecular level as well as the ecological consequences of the application should be considered to be of outstanding importance. In these topics, the developments related to active ingredients, which are considered traditional and used in doses of 0.2-5 kg-ha, can also provide important results; especially regarding the discovery of the causes of acquired resistance to drugs. Instead of restricting the use of chemicals, it is more appropriate to urge support for developments that provide the opportunity for product exchange and the research that underpins this. This applies both to the modernization of use (improvement of target delivery methods, development of more effective drug forms, etc.), and to the development of new, more effective, and selective active ingredients.

Plethora of new substances enter the human environment, and among them, those that are easily absorbed into living cells are particularly vulnerable. Plant protection products are like this since the basic part of their effectiveness is easy entry into the cell. In Hungary, over 100 different criteria must be met to obtain a license for experimental use. Some of these requirements seem superfluous to the superficial observer or outsider. However, the microbes compete in biocoenoses, and removing one element from the plant/microbe consortium opens the door for other organisms. Extremely thorough and careful investigations help to recognize it in time. Developers are under enormous pressure, partly from aggressive financial capital and partly from politicians seeking the favor of consumers (Figure 10).

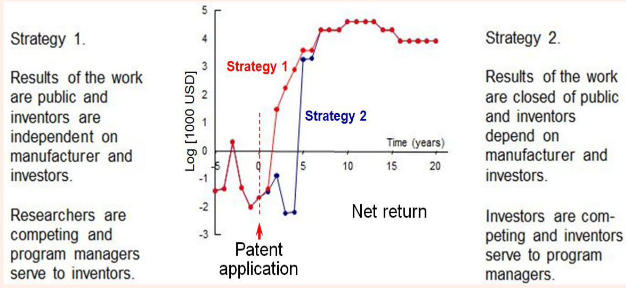

Figure 10: Financial effectiveness of various strategies in pesticide development.

Source: Imported of Oros et al., 2003 [17]

Note: The calculation was made on the example of development of new agricultural fungicide KF-73, where 40 USD/kg of commercial price of preparation was considered.

Nevertheless, the experiences of the past century's development so far show that science was able to provide adequate answers to all the questions raised in crop protection (Figure 4). Development work is also hindered by new challenges. The recently developed screening methods allow the versatile and simultaneous examination of the physiological effects of synthetic molecules. However, the emergence of the informatics market unfortunately hinders the scientific discussion of these new screening methods and the new data obtained due to patent rights. In past decades two different strategies of pesticide development have evolved (Figure 10), and according to our calculations, the costs of the development will pay off faster following the opened strategy. We can hope that the widespread availability of knowledge about the influence of plant-microbe interactions will accelerate evolution of our imaginations about the organization of microbial consortia and their functional interaction with macrobial partners, as well as initiates elaboration of new theory of plant pathology, that is a prerequisite of the development of rapid responses to new challenges in pest management.

Conclusion

Based on our preliminary investigations, we assume that it is possible to design molecules with a selective bactericidal effect at the genus level with high therapeutic value; and in our opinion, this degree of selectivity is the minimum requirement for their use in pest management to avoid undesirable effects on the plant associated microbial consortium. The investigation of the side effects of pesticides should be examined more thoroughly than before even in the case of sublethal exposures, especially regarding the nature of their interaction with xenobiotics used for other purposes. Within this, it is necessary to pay attention primarily both to the drugs used *per os* and the compounds that have entered to the food chain. The broadest access to knowledge about the effects of xenobiotics on living organisms must be made possible. In this respect the main conclusion might be drowned; it is necessary to expand the teaching of ecological knowledge at all educational levels which helps reduce concerns about pesticide use.

Conflict of Interest: The author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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