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Existing potentials in Insect Growth Regulators (IGR) for crop pest control

Potenciais existentes em inseticidas reguladores do desenvolvimento de insetos (Insect Growth Regulators – IGR) para o controle de pragas de lavouras

Potenciales existentes en insecticidas reguladores del crecimiento de insectos (Insect Growth Regulators – IGR) para el control de plagas de cultivo

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Abstract
The aim of this review is to explore the potentials existing in insecticides that are considered Insect Growth Regulators (IGR) for the control of insects considered crop pests, with an observation of the main mechanisms of neuroendocrine modifications, development and viability of the species used as study models. The data search on digital platforms, as well as the screening of materials about crop pests, resulted in 74 IGR references and their potentials. The analysis of the information found demonstrated a greater use in works of compounds belonging to chitin synthesis inhibitors class; and orders such as Hemiptera, Lepidoptera, Coleoptera, Orthoptera, Thysanoptera and Diptera were represented in the studies. The main types of activities reunited were morphological and anatomical modifications, reproductive modifications, alterations in developmental stage, alterations in developmental period, ovicidal activity, larvicidal/ninficidal activity and fagoinhibition. The congregated knowledge about the main pests used as study models, the main IGRs compounds and their biological potentials allow an evaluation of their use as an informative source for crop pest control methods.
Keywords: Ovicide; Larvicide; Morphological modifications; Reproductive modifications; Fagoinhibition.

Resumo
O objetivo da presente revisão foi a exploração dos potenciais existentes em inseticidas considerados reguladores do desenvolvimento de insetos (Insect Growth Regulators – IGR) para o controle de insetos pragas de lavouras, havendo uma observação dos principais mecanismos de alterações neuroendócrinas, desenvolvimento e viabilidade das espécies utilizadas como modelos de estudo. A busca de dados em plataformas digitais, assim como a realização de uma triagem de informações sobre pragas agrícolas, resultou na aquisição de 74 referências sobre o potencial de IGRs. A análise das informações encontradas demonstrou uma maior utilização nos trabalhos de compostos pertencentes à classe dos inibidores de síntese de quitina; e ordens como Hemiptera, Lepidoptera, Coleoptera, Orthoptera, Thysanoptera e Diptera foram representadas nos estudos. Os principais tipos de atividades reunidas foram alterações morfológicas e anatômicas, alterações reprodutivas, alterações em estágios de desenvolvimento, alterações no período de desenvolvimento, atividade ovicida, atividade larvicida/ninficida e inibição de alimentação. O conhecimento reunido sobre as principais pragas utilizadas como modelos de estudo, e os principais compostos IGRs e seus potenciais biológicos permitem uma avaliação sobre o seu uso como fonte de informação para medidas de controle de pragas agrícolas.
Palavras-chave: Ovicida; Larvicida; Alterações morfológicas; Alterações reprodutivas; Inibição de alimentação.

Resumen
El objetivo de esta revisión fue explorar los potenciales existentes en insecticidas considerados reguladores del crecimiento de los insectos (Insect Growth Regulators - IGR) para el control de insectos plaga de cultivos, con una observación de los principales mecanismos de modificaciones neuroendocrinas, desarrollo y viabilidad de las especies utilizadas como modelos de estudio. La búsqueda de datos en plataformas digitales, así como un cribado de información sobre plagas agrícolas, resultó en la adquisición de 74 referencias sobre el potencial de los IGR. El análisis de la información encontrada demostró un uso más grande en el trabajo de compuestos pertenecientes a la clase de inhibidores de la síntesis de quitina; y órdenes como Hemiptera, Lepidoptera, Coleoptera, Orthoptera, Thysanoptera y Diptera estuvieron representadas en los estudios. Los principales tipos de actividades reunidas fueron

modificaciones morfológicas y anatómicas, modificaciones reproductivas, modificaciones en las etapas del desarrollo, modificaciones en el período de desarrollo, actividad ovicida, actividad larvicida/ninficida e inhibición de la alimentación. El conocimiento recopilado sobre las principales plagas utilizadas como modelos de estudio, y los principales compuestos de IGR y sus potenciales biológicos permiten evaluar su uso como fuente de información para las medidas de control de plagas agrícolas.

Palabras clave: Ovicida; Larvicida; Modificaciones morfológicas; Modificaciones reproductivas; Inhibición de la alimentación.

1. Introduction

The agricultural sector demonstrates a great contribution in the scope of productivity, being able to be expressed in values relative to ¾ of worldwide economy (FAO, 2013). An insect, when is considered an agricultural pest, has an abundance in its density that cause financial losses in important crops. Sharma et al. (2017) emphasize the damage caused by agricultural pests on a global scale, with an estimated loss of 18-20% in annual production and $ 470 billion.

The use of chemical substances for insect population control, which has as one of its purposes the improvement of economic investment, can often result in environmental toxicity problems (Moreira, et al., 1996). The scientific progress in the last decades have made possible the exploration of alternative methods regarding the regulation of insect development, based on compounds with mechanisms of greater selectivity and less toxicity to non-target organisms; which could overcome problems caused by the use of organochlorine and organophosphate insecticides, characterized as insecticides of the first generations (Faria, 2009).

Insect growth regulators (IGRs) have a role in regulating essential physiological processes in insects; they are not necessarily toxic and may alter specific pathways of hormonal control that are related to molting, metamorphosis and reproduction (Tunaz & Uygun, 2004). Since its potential discovery, credited to the "paper factor" related by Sláma & Williams (1965), IGRs have been commercialized at an industrial level and widely used in pest control. In spite of several of these compounds have been explored in studies, there are few materials that gather information about these substances in a concise way and that show their evaluated potentials, mainly about the study of insect control in agriculture.

Therefore, the aim of this article is to carry out a review of IGRs use in the control of insects considered crop pests, based on the analysis of mechanisms concerning changes in hormonal and developmental pathways, as well as the exploration of the main potentials of existing biological activities, and the quantification and qualification of analyzed data.

2. Methodology

For the data search, which was made from 2018 to 2020, the platforms Periódicos Capes, National Center for Biotechnology Information (NCBI) and Scientific Electronic Library Online (SciELO) were used. A combination of terms from the main classes of IGRs, mechanisms of action and potentials against agricultural pests was used, such as "ecdysteroid agonists against agricultural pests", where there was an exchange of only the first and second terms according to the IGR class.

Due to the great amount of results, an initial screening was realized with the selection of works that only studied agricultural pests, being discarded sources that used model insects in classical studies of insect physiology [e.g. *Bombyx mori* (Linnaeus, 1758) (Lepidoptera: Bombycidae)], genetic [e.g. *Drosophila melanogaster* (Diptera: Drosophilidae)], insects considered urban pests [e.g. *Cryptotermes brevis* (Walker, 1853) (Isoptera: Kalotermitidae)] and vector disease insects [e.g. *Rhodnius prolixus* (Hemiptera: Reduviidae)]. Subsequently, a second screening was carried out to reduce the number of sources of IGRs use in agricultural pests, excluding works that took into account insects considered stored product pests [e.g. *Trobolium castaneum* (Herbst, 1797) (Coleoptera: Tenebrionidae)], choosing only studies with models considered crop pests. The digital platforms Centre for Agriculture and Bioscience International (CABI), Agrolink and BugGuide were used to ascertain the classification of species in crop pests, according to criteria of eating habits, damages in plantations and parts of plants such as leaves, stems, branches, sprouts, tubers, seeds, fruits and flowers.

The study gathered a total of 107 references and, among them, 74 are specifically about the potential of IGRs in insects considered crop pests. The information includes studies ranging from classic works dating from 1934 to studies of 2019.

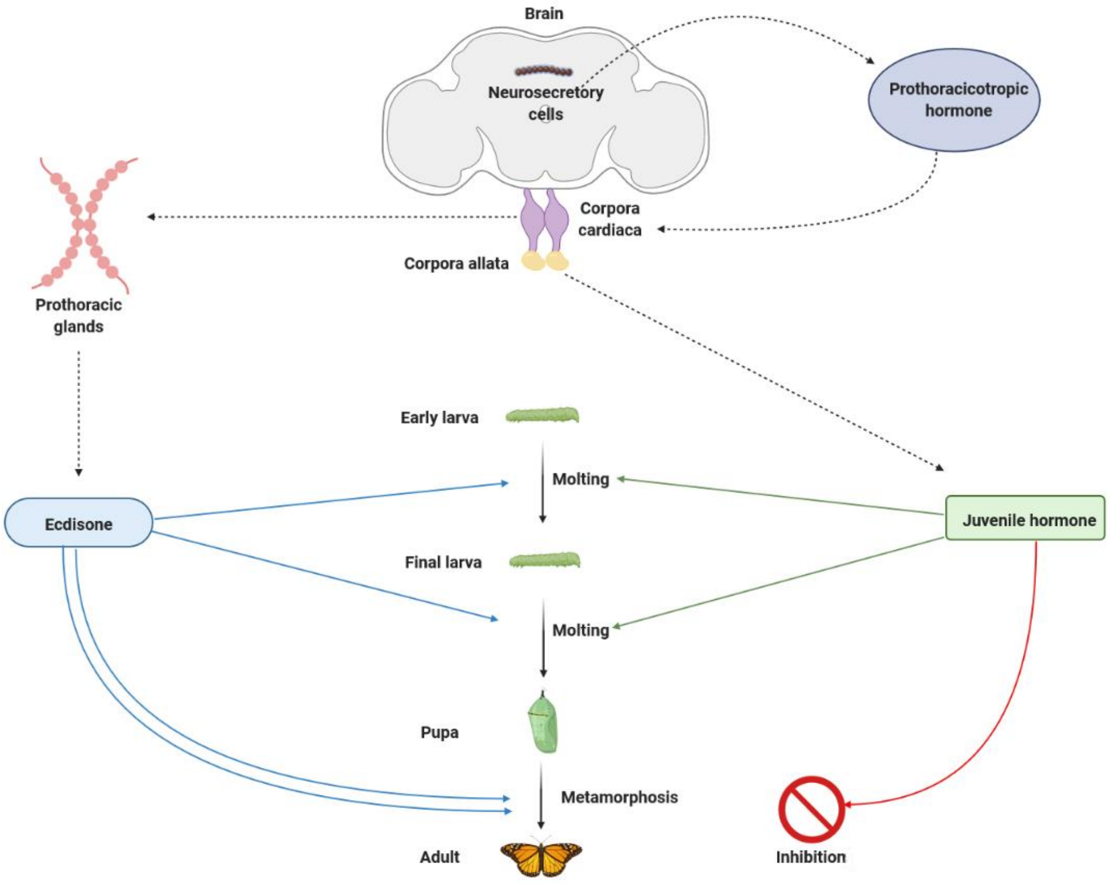
3. Results and Discussion

Hormonal control modifications by IGRs activities

Insects have physiological processes that are directly related to endocrine centers and integrated and correlated hormonal responses. In neuroendocrine control, represented in Figure 1, the neurosecretory cells (NSC) present in the insect brain consist of neurons that are specialized in hormone production; and that project their axons into a series of endocrine glands and neurohemal organs (Harstenstein, 2006). While the endocrine glands are structures adapted to produce and release hormones in the circulatory system, neurohemal organs are based on the storage of hormone until the neuroendocrine pathways signals mediate its products release (Gullan & Cranston, 2014).

The prothoracicotropic hormone (PTTH) is produced by NCS and stored in the neurohemal organ corpora cardiaca (CC) and, later, it will be released to promote the stimulation of the prothoracic glands and the consequent production of ecdysone (Ec). This Ec is in its inactive form, being converted to a 20-hydroxyecdysone (20HE) in the epidermal cells by 20-hydroxylase (Song, et al., 2017), which will circulate in the hemolymph and start a new cycle of division of the epidermal cells to form a new cuticle (Klowden, 2013). The endocrine gland corpora allata (CA) is responsible for the production and release of juvenile hormone (JH), primarily described by Wigglesworth (1934), consisting of a sesquiterpene with the function of inhibiting genes that promote the development of adult characteristics, participating in processes of molting and metamorphosis (Klowden, 2013; Gullan & Cranston, 2014) and, later, in reproductive mechanisms. According to Klowden (2013), the presence of Ec results, in a process of molting, the same type of cuticle; while the absence of JH and the presence of Ec stimulate the reprogramming of epidermal cells to produce specific proteins for the next stage and the completion of metamorphosis process.

Figure 1 - Schematic representation of a neuroendocrine control in insects.



Source: Created in Biorender.com.

Substances that are characterized as IGRs can interfere with the neuroendocrine balance existing in insects, acting as agonists or antagonists of the hormones involved in the main physiological processes of development. Among the IGRs, there are juvenoids, anti-juvenoids, ecdysteroid agonists and antagonists, chitin synthesis inhibitors and PTTH synthesis inhibitors.

Juvenoids, also known as JH mimics or JH agonists, can prolong nymph/larva/pupa development period by increasing JH levels (Gallo, et al., 2002). Examples of JH analogues are substances such as methoprene and pyriproxyfen, and their capacity for prolonging the larval period is proven (Miranda, et al., 2002).

Anti-juvenoids, also known as JH antagonists or precocenes, were primarily recognized by Bowers et al. (1976) in studies with *Oncopeltus fasciatus* (Dallas, 1852) (Hemiptera: Lygaeidae), observing effects of nymphs with early development in adults, and sterile adults. They are able to interfere in the synthesis of JH through injuries to CA, maintaining high levels of PTTH and stimulating the reprogramming of epidermal cells for an early metamorphosis process (Gallo et al., 2002). Hypotheses suggest that there is a competition between anti-juvenoids and JH in the carrier proteins binding, reducing the activity of JH (Staal, 1986; Tunaz & Uygun, 2004). Reports in the literature express the role of precocenes in CA degeneration (Ergen, 2001; Gotoh, et al., 2008); and allatostatins in inhibiting JH synthesis in CA (Woodhead et al., 1989).

Ecdysteroid agonists are capable of causing premature and incomplete molting in insects, being represented by substances such as methoxyfenozide and tebufenozide. They can exert their toxicity by binding to the ecdysone EcR receptor, competing with 20HE (Berguiche, et al., 2008). Studies demonstrate its toxic and ovicidal activities, mainly in Lepidoptera and Coleoptera (Gallo, et al., 2002; Borchert, et al., 2004; Berghiche, et al., 2008).

Ecdysteroid antagonists, according to Dinan (1996), prevent ecdysteroids from inducing responses or blocking induced responses; being recognized by these potential compounds as cucurbitacins and withanolides (Dinan, 1996, 1997; Sarker, et al., 1997; Savchenko, 2000).

Chitin synthesis inhibitors (CSI) comprise a group of substances called benzoylphenylureas, with an inhibitory mechanism in chitin synthetase (Gallo, et al., 2002). According to Tunaz and Uygun (2004), this inhibition can occur in three ways: by inhibiting chitin synthase; by inhibiting proteases that activate chitin synthase; and by inhibiting UDP-N-acetylglucosamine membrane transport. Among the various types of substances known for CSI activity, there are diflubenzuron, triflumuron and lufenuron.

PTTH synthesis inhibitors have their potential demonstrated, mainly, in studies with azadirachtin, a tetra-nor-triterpenoid derived from the neem tree *Azadirachta indica* (Meliaceae) (Viegas Júnior, 2003). It has a phagoinhibitory action that interferes with the endocrine regulation in the CC of insects, reducing PTTH levels and inhibiting metamorphosis (Viegas Júnior, 2003; Faria, 2009). Species of Lepidoptera, Coleoptera, Hemiptera and Hymenoptera have sensitivity to azadirachtin (Mordue & Nisbet, 2000).

Compounds that act as IGRs have a wide range of action in insect control, representing potential regulators for the development of disease vectors, urban pests and storage products pests. IGRs activities in crop pests can demonstrate several types of biological potentials that will be elucidated below and are also organized and visualized in the Table 1.

Table 1 – Reference list of works that explore the use of Insect Growth Regulator compounds to control insects considered crop pests, and their activities. IGR – Insect Growth Regulator; CSI – Chitin Synthesis Inhibitor; JH – Juvenile Hormone; PTTH – Prothoracicotropic Hormone.

Authors	Crop pest species estudied	Compounds used – IGR class	Activities
Adel & Sehnal (2000)	*Spodoptera littoralis* (Boisduval, 1833) (Lepidoptera: Noctuidae)	Methoxyfenozide, Tebufenozide – Ecdysteroid agonists Azadirachtin – PTTH inhibitor	Larvicide, Reproductive modifications, Alteration in developmental period, Fagoinhibition
Alavo et al. (2011)	*Helicoverpa armigera* (Hubner, 1808) (Lepidoptera: Noctuidae)	Methoxyfenozide – Ecdysteroid agonist	Larvicide
Al-Mokhlef et al. (2012)	*Schistocerca gregaria* (Foskal, 1775) (Orthoptera: Acrididae)	Teflubenzuron – CSI	Morphological modifications
Alyokhin et al. (2008)	*Leptinotarsa decemlineata* Say (1824) (Coleoptera: Chrysomelidae)	Novaluron – CSI	Ovicide, Reproductive modifications
Amiri et al. (2010)	*Eurygaster integriceps* (Puton, 1881) (Hemiptera: Scutelleridae)	Precocene I – JH antagonist	Ninficide, Reproductive modifications, Morphological and anatomical modifications
Andrade et al. (2013)	*Aphis gossypii* Glover (1877) (Hemiptera: Aphididae)	Azadirachtin – PTTH inhibitor	Ninficide
Ascher & Eliyahu (1988)	*Bemisia tabaci* (Gennadius, 1889) (Hemiptera: Aleyrodidae)	S-31183 (SK-591) – JH agonist	Ovicide
	Spodoptera littoralis (Boisduval, 1833) (Lepidoptera: Noctuidae)		
Ascher et al. (1987)	*Epilachna varivestis* (Mulsant, 1850) (Coleoptera: Coccinellidae)	Withanolide E, 2,3-dihydrowithanolide E – Ecdysteroid antagonists	Fagoinhibition
	Spodoptera littoralis (Boisduval, 1833) (Lepidoptera: Noctuidae)		
Atta et al. (2015)	*Oxycarenus hyalinipennis* (Costa, 1847) (Hemiptera: Lygaeidae)	Lufenuron – CSI	Ninficide
Ayyanath et al. (2015)	*Myzus persicae* (Sulzer, 1776) (Hemiptera: Aphididae)	Precocene I – JH antagonist	Reproductive modifications

Bado et al. (2004)	*Ceratitis capitata* Wiedemann (1824) (Diptera: Tephritidae)	Withanolides isolated from *Salpichroa origanifolia* (Lam.) Bail (Solanaceae) – Ecdysteroid antagonists	Larvicide
Bakr et al. (2010)	*Spodoptera littoralis* (Boisduval, 1833) (Lepidoptera: Noctuidae)	Flufenoxuron – CSI	Reproductive modifications, Morphological modifications
Belai & Fekete (2003)	*Dysdercus cingulatus* (Fabricius, 1775) (Hemiptera: Pyrrhocoridae)	Azole compounds – Ecdysteroid antagonists	Morphological modifications
Bernardi et al. (2012)	*Chaetosiphon fragaefolli* (Crockerell, 1901) (Hemiptera: Aphididae)	Azadirachtin – PTTH inhibitor	Reproductive modifications, Morphological modifications
Bertuso et al. (2002)	*Nilaparvata lugens* (Stal, 1854) (Hemiptera: Delphacidae)	Precocene II – JH antagonist	Alteration in developmental period
Bitsadze et al. (2013)	*Locusta migratoria* (Linnaeus, 1758) (Orthoptera: Acrididae)	Diflubenzuron – CSI	Larvicide
Boina et al. (2009)	*Diaphorina citri* Kuwayama (1908) (Hemiptera: Liviidae)	Pyriproxyfen – JH agonist	Ovicide, Ninficide, Morphological modifications
Bransby-Williams (1971)	*Dysdercus cardinalis* (Gerstaecker, 1873) (Hemiptera: Pyrrhocoridae)	Methyl farnesoate dihydrochloride – JH agonist	Reproductive modifications, Alteration in developmental stage
Carlson et al. (2011)	*Cydia pomonella* (Linnaeus, 1758) (Lepidoptera: Tortricidae)	Methoxyfenozide – Ecdysteroid agonist	Larvicide
	Helicoverpa zea (Boddie, 1850) (Lepidoptera: Noctuidae)		
	Ostrinia nubilalis (Hubner, 1796) (Lepidoptera: Noctuidae)		
	Spodoptera exigua (Hubner, 1808) (Lepidoptera: Noctuidae)		
	Spodoptera frugiperda (J.E. Smith, 1797) (Lepidoptera: Noctuidae)		
	Trichoplusia ni (Hubner, 1803) (Lepidoptera: Noctuidae)		
Chenevert et al. (1980)	*Schistocerca gregaria* (Foskal, 1775) (Orthoptera: Acrididae)	Precocenes I e II – JH antagonist	Larvicide, Alteration in developmental period

Cirigliano et al. (2008)	*Ceratitis capitata* Wiedemann (1824) (Diptera: Tephritidae)	Withanolide E, 4-ß-hydroxiwithanolide E – Ecdysteroid antagonists	Larvicide
Costa et al. (2017)	*Anthonomus grandis* Boheman (1843) (Coleoptera: Curculionidae)	Lufenuron – CSI	Reproductive modifications
Cotton & Anstee (1991)	*Locusta migratoria* (Linnaeus, 1758) (Orthoptera: Acrididae)	Methoprene – JH agonist	Morphological modifications
Critchley & Campion (1971)	*Dysdercus fasciatus* (Signoret, 1861) (Hemiptera: Pyrrhocoridae)	Methyl farnesoate dihydrochloride – JH agonist	Reproductive modifications, Morphological modifications, Alteration in developmental stage
Eid et al. (1988)	*Schistocerca gregaria* (Foskal, 1775) (Orthoptera: Acrididae)	Precocene II – JH antagonist	Reproductive modifications, Morphological modifications, Alteration in developmental period
Eisa et al. (1991)	*Ceroplastes floridensis* Comstock (1881) (Hemiptera: Coccidae)	Hexaflumuron, Teflubenzuron – CSI Fenoxycarb, Pro-done, R-20458, dofenapyn – JH agonists	Ninficide, Reproductive modifications
Eizaguirre et al. (2007)	*Sesamia nonagrioides* (Lefébvre, 1827) (Lepidoptera: Noctuidae)	Methoxyfenozide – Ecdysteroid agonist	Morphological modifications, Fagoinhibition
El-Sheik et al. (2016)	*Spodoptera frugiperda* (J.E. Smith, 1797) (Lepidoptera: Noctuidae)	Methoprene, Pyriproxyfen, Fenoxycarb – JH agonists	Larvicide, Morphological modifications
	Spodoptera littoralis (Boisduval, 1833) (Lepidoptera: Noctuidae)		
Fang et al. (2017)	*Laodelphax striatellus* (Fallén, 1826) (Hemiptera: Delphacidae)	Kanakugiol – JH antagonist	Ninficide
Ghazawy (2012)	*Schistocerca gregaria* (Foskal, 1775) (Orthoptera: Acrididae)	Lufenuron – CSI	Reproductive modifications
Gijswijt et al. (1979)	*Pieris brassicae* (Linnaeus, 1758) (Lepidoptera: Pieridae)	Diflubenzuron – CSI	Morphological modifications
Gokçe et al. (2008)	*Cydia pomonella* (Linnaeus, 1758) (Lepidoptera: Tortricidae)	Novaluron – CSI	Reproductive modifications
Guyer & Neumann (1988)	*Heliothis virescens* (Fabricius, 1781) (Lepidoptera: Noctuidae)	Diflubenzuron, Chlorfluazuron – CSI	Larvicide, Morphological modifications
	Spodoptera littoralis (Boisduval, 1833) (Lepidoptera: Noctuidae)		

Hales & Mittler (1981)	*Myzus persicae* (Sulzer, 1776) (Hemiptera: Aphididae)	Precocene III – JH antagonist	Morphological modifications, Alteration in developmental period
Hardie (1986)	*Acyrthosiphon pisum* (Harris, 1776) (Hemiptera: Aphididae)	Precocenes I e III – JH antagonists	Morphological modifications, Alteration in developmental period
	Aphis fabae Scopoli (1763) (Hemiptera: Aphididae)		
Hardie (1996)	*Acyrthosiphon pisum* (Harris, 1776) (Hemiptera: Aphididae)	Precocene derivatives 2,2-dimethylchroman and 2,2-dimetilchromene – JH antagonists	Morphological modifications
Hoffmann et al. (2008)	*Cronotrachelus nenuphar* (Herbst, 1906) (Coleoptera: Curculionidae)	Novaluron – CSI	Ovicide
Hosseinzadeh & Delkhoom (2013)	*Leptinotarsa decemlineata* (Say, 1824) (Coleoptera: Chrysomelidae)	Lufenuron – CSI	Larvicide, Morphological and anatomical modifications
Ishaaya et al. (1995)	*Spodoptera littoralis* (Boisduval, 1833) (Lepidoptera: Noctuidae)	Methoxyfenozide, Tebufenozide – Ecdysteroid agonists	Larvicide, Reproductive modifications
Joseph (2017)	*Bagrada hilaris* (Burmeister, 1835) (Hemiptera: Pentatomidae)	Novaluron, Diflubenzuron – CSI Azadirachtin – PTTH inhibitor	Ninficide, Reproductive modifications
Joseph (2019)	*Stephanitis pyrioides* (Scott, 1874) (Hemiptera: Tingidae)	Pyriproxyfen, Buprofezin – JH agonists Azadirachtin – PTTH inhibitor Novaluron – CSI	Reproductive modifications
Kafi-Farashah et al. (2018)	*Eurygaster integriceps* (Puton, 1881) (Hemiptera: Scutelleridae)	Precocene I – JH antagonists	Ovicide, Morphological and anatomical modifications
Karimzadeh et al. (2007)	*Leptinotarsa decemlineata* Say (1824) (Coleoptera: Chrysomelidae)	Diflubenzuron, Cyromazine, Lufenuron, Hexaflumuron, Triflumuron – CSI	Morphological and anatomical modifications
Khafagi & Hegazi (1999)	*Spodoptera littoralis* (Boisduval, 1833) (Lepidoptera: Noctuidae)	Precocene II – JH antagonists	Morphological modifications
Khajepour et al. (2012)	*Ephestia figulilella* (Gregson, 1871) (Lepidoptera: Pyralidae)	Hexaflumuron, Lufenuron – CSI	Larvicide, Morphological modifications, Alteration in developmental stage

Khan & Qamar (2011)	*Dysdercus koenigii* (Fabricius, 1775) (Hemiptera: Pyrrhocoridae)	Flucycloxuron – CSI	Reproductive modifications, Morphological and anatomical modifications
Khan & Qamar (2012)	*Dysdercus koenigii* (Fabricius, 1775) (Hemiptera: Pyrrhocoridae)	Flucycloxuron – CSI	Reproductive modifications
Kim et al. (2011)	*Cydia pomonella* (Linnaeus, 1758) (Lepidoptera: Tortricidae)	Novaluron – CSI	Reproductive modifications
Kontogiannatos et al. (2014)	*Sesamia nonagrioides* (Lefébvre, 1827) (Lepidoptera: Noctuidae)	Tebufenozide, Bisphenol A – Ecdysteroid agonist	Morphological modifications, Alteration in developmental period
Kubota (1989)	*Thrips palmi* Karny (1925) (Thysanoptera: Thripidae)	Diflubenzuron, Teflubenzuron, Chlorfluazuron, Flufenoxuron and Cyromazine – CSI	Ovicide, Larvicide
Li et al. (2014)	*Aphis craccivora* Koch (1854) (Hemiptera: Aphididae)	Hexaflumuron, Chlorfluazuron, Etoxazole – CSI	Larvicide, Ninficide
	Plutella xylostella (Linnaeus, 1758) (Lepidoptera: Plutellidae)		
	Spodoptera exigua (Hubner, 1808) (Lepidoptera: Noctuidae)		
Mahmoudvand & Moharramipour (2015)	*Plutella xylostella* (Linnaeus, 1758) (Lepidoptera: Plutellidae)	Fenoxycarb – JH agonist	Larvicide, Reproductive modifications, Alteration in developmental period
Martinez & Emden (2001)	*Spodoptera littoralis* (Boisduval, 1833) (Lepidoptera: Noctuidae)	Azadirachtin – PTTH inhibitor	Larvicide, Morphological modifications
Mckenna et al. (2013)	*Phyllocnistis citrella* (Stainton, 1856) (Lepidoptera, Gracillariidae)	*Melia azedarach* L. (Meliaceae) extracts and neem oil – PTTH inhibitor	Larvicide
Meisner et al. (1986)	*Earias insulana* (Boisduval, 1833) (Lepidoptera: Noctuidae)	Diflubenzuron, PH 60-43, Penfluron, PH 60-45, Triflumuron, Chlorfluazuron, Teflubenzuron, XRD-473, Dowco 439 – CSI	Morphological modifications
Meng et al. (2018)	*Leptinotarsa decemlineata* Say (1824) (Coleoptera: Chrysomelidae)	Teflubenzuron – CSI	Morphological and anatomical modifications, Fagoinhibition

Mordue & Nisbet (2000)	*Pieris brassicae* (Linnaeus, 1758) (Lepidoptera: Pieridae)	Azadirachtin – PTTH inhibitor	Morphological modifications, Fagoinhibition
	Schistocerca gregaria (Foskal, 1775) (Orthoptera: Acrididae)		
Pavan et al. (2005)	*Lobesia brotana* (Denis & Schiffermuller, 1775) (Lepidoptera: Tortricidae)	Lufenuron – CSI	Larvicide
Pedersen (1978)	*Locusta migratoria* (Linnaeus, 1758) (Orthoptera: Acrididae)	Precocene I – JH antagonist	Morphological modifications, Alteration in developmental period
Pener et al. (1986)	*Locusta migratoria* (Linnaeus, 1758) (Orthoptera: Acrididae)	Precocene III – JH antagonist	Ovicide
Perez-Farinos et al. (1998)	*Aubeonymus mariaefranciscae* (Roudier, 1981) (Coleoptera: Curculionidae)	Hexaflumuron – CSI	Larvicide, Reproductive modifications
Seth et al. (2004)	*Spodopetra litura* (Fabricius, 1775) (Lepidoptera: Noctuidae)	Tebufenozide, RH-5849 – Ecdysteroid agonists	Reproductive modifications
Singh & Kumar (2011)	*Papilio demoleus* (Linnaeus, 1758) (Lepidoptera: Papilionidae)	Pyriproxyfen – JH agonist	Morphological and anatomical modifications, Alteration in developmental period
Singh & Kumar (2015)	*Spodopetra litura* (Fabricius, 1775) (Lepidoptera: Noctuidae)	Pyriproxyfen, Diafenolan – JH agonists	Morphological and anatomical modifications, Alteration in developmental stage, Alteration in developmental period
Suchy et al. (1968)	*Dysdercus chaquensis* Freiberg (1947) (Hemiptera: Pyrrhocoridae)	Derivative compounds of p-(1,5-dimethylhexyl)benzoic acid – JH agonist	Ninficide
	Dysdercus cingulatus (Fabricius, 1775) (Hemiptera: Pyrrhocoridae)		
	Dysdercus discolor Walker (Hemiptera: Pyrrhocoridae)		
	Dysdercus intermedius (Distant, 1890) (Hemiptera: Pyrrhocoridae)		
	Dysdercus superstitiosus (Fabricius, 1775) (Hemiptera: Pyrrhocoridae)		

Sun et al. (2003)	*Cydia pomonella* (Linnaeus, 1758) (Lepidoptera: Tortricidae)	Methoxyfenozide, Tebufenozide – Ecdysteroid agonists	Reproductive modifications
Tail et al. (2008)	*Schistocerca gregaria* (Foskal, 1775) (Orthoptera: Acrididae)	Diflubenzuron – CSI	Reproductive modifications
Tallamy et al. (1997)	*Acyrthosiphon pisum* (Harris, 1776) (Hemiptera: Aphididae)	Cucurbitacin B – Ecdysteroid antagonist	Fagoinhibition
	Cerotoma trifurcata (Foster) (Coleoptera: Chrysomelidae)		
	Corythucha ciliata (Say, 1832) (Hemiptera: Tingidae)		
	Gargaphia solani (Heidemann 1914) (Hemiptera: Tingidae)		
	Ostrinia nubilalis (Hubner, 1796) (Lepidoptera: Pyralidae)		
	Popillia japonica Newman, 1841 (Coleoptera: Scarabaeidae)		
	Peregrinus maidis (Ashmead, 1890) (Hemiptera: Delphacidae)		
	Spodoptera exigua (Hubner, 1808) (Lepidoptera: Noctuidae)		
	Trichoplusia ni (Hubner, 1803) (Lepidoptera: Noctuidae)		
Triseleva (2003)	*Locusta migratoria* (Linnaeus, 1758) (Orthoptera: Acrididae)	Precocenes – JH antagonists	Fagoinhibition
	Myzus persicae (Sulzer, 1776) (Hemiptera: Aphididae)		
	Trialeurodes vaporariorum (Westwood, 1856) (Hempitera: Aleyrodidae)		
Wang & Sehnal (2002)	*Schistocerca gregaria* (Foskal, 1775) (Orthoptera: Acrididae)	Methoxyfenozide – Ecdysteroid agonist	Reproductive modifications

Xu et al. (2015)	*Spodopetra litura* (Fabricius, 1775) (Lepidoptera: Noctuidae)	Pyriproxyfen – JH agonist	Reproductive modifications
Yousaf et al. (2018)	*Aphis gossypii* Glover (1877) (Hemiptera: Aphididae)	Cucurbitacin B – Ecdysteroid antagonist	Reproductive modifications
Zarate et al. (2009)	*Spodoptera frugiperda* (J.E. Smith, 1797) (Lepidoptera: Noctuidae)	Methoxyfenozide - Ecdysteroid agonist	Larvicide, Morphological modifications, Alteration in developmental period
Zhang et al. (2016)	*Bradysia odoriphaga* (Yang and Zhang, 1985) (Diptera: Sciaridae)	Chlorfluazuron, Hexaflumuron, Diflubenzuron and Cyromazine – CSI	Morphological and anatomical modifications, Fagoinhibition

Source: Authors.

Data quantification and qualification

The present review demonstrates 45 compounds characterized as IGRs, being cited around 119 times over the 74 references used to compose the study of potentials. Among the existing classes of regulators, CSI proved to be the most explored by the works, accounting for 45.38% of substances with explored potentials. They are compounds that have been widely commercialized for some decades and that show their activities of interference in chitin formation, as well as in insects reproduction and development (Merzendorfer, 2012). Thereafter are JH analogs (16.81%), JH antagonists (12.60%), ecdysteroid agonists (11.76%), azadirachtin and derivatives as PTTH inhibitor representatives (6.72%) and ecdysteroid antagonists (6.72%). Among the most cited substances, diflubenzuron was observed, being represented in nine works; methoxyfenozide, being explored in eight studies; lufenuron and azadiractin, being cited in seven studies each; and novaluron, hexaflumuron, precocene I and pyriproxifen, present in six studies each.

The information obtained about the crop pests used as models in the different studies allows an observation about the main orders and species mentioned. Hemiptera was the largest order explored in the works, with 45.76% of representativeness, followed by Lepidoptera with 33.90%; while Coleoptera obtained 11.86% of expression in the studies, Orthoptera 3.39%, Diptera also 3.39% and Thysanoptera 1.69% of presence. The orders present in this review coincide with those reported by Culliney (2014), which characterizes them as being the most important orders for agricultural pests. Among the species, *Spodoptera littoralis* (Boisduval, 1833) (Lepidoptera: Noctuidae) was the most used in the studies, being mentioned in nine articles, which can characterize its importance as a source of study for control methods while it demonstrates to be one of the lepidopterans with the greatest economic impact in plantations of cotton, tomatoes, tobacco and maize (CABI, 2019). Orthoptera demonstrated great relevance in the studies, being represented by insects inserted in economic and historical contexts due to their polyphagy and migration capabilities. *Schistocerca gregaria* (Foskal, 1775) (Orthoptera: Acrididae) and *Locusta migratoria* (Linnaeus, 1758) (Orthoptera: Acrididae) appeared in seven and five studies, respectively.

The mechanisms of action exerted by IGRs on crop pests revealed a diversity of biological potentials. Larvicidal/ninficidal potentials were demonstrated in 27.89% of the results, and morphological/anatomical modifications 23.81%, these being the two major activities found. Reproductive modifications accounted for 18.37% of the results, while fagoinhibitive activities showed 12.24% of the results. Alterations in the development period appeared with 8.84% of representativeness; ovicidal potential were observed in 6.12% of the results; and 2.72% of the data analyzed correspond to alterations in stages of development.

Biological potential of IGRs in crop pests

Ovicidal potential

There are methods based on the applicability of IGRs in eggs, in order to assess the effects on their viability and hatching capacity. Juvenoids are types of substances that can express these activities. Ascher and Eliyahu (1988) analyzed the ovicidal activity of S-31183 (SK-591) in the insects *Bemisia tabaci* (Gennadius, 1889) (Hemiptera: Aleyrodidae), known as whitefly, and *S. littoralis*; demonstrating an absence of hatching eggs of *B. tabaci* that were treated, and a mortality higher than 90% of eggs of *S. littoralis* treated with concentrations below 0.05 ppm. Pyriproxifen demonstrated a hatching inhibition of approximately 70% of eggs in a treatment with *Diaphorina citri* Kuwayama (1908) (Hemiptera: Liviidae), the Asian citrus psyllid (Boina, et al., 2009).

Precocenes may also demonstrate ovicidal potential through their mechanisms of JH antagonism, and by acting at different stages of egg development. Pener et al. (1986) evidenced the reduction of JH levels in precocene III treatments in 10-

day-old eggs of *L. migratoria*. Kafi-Farashah et al. (2018), in analyzes of precocene I activity in *Eurygaster integriceps* (Puton, 1881) (Hemiptera: Scutelleridae), the Sunn pest, showed greater effects of mortality and susceptibility in older eggs.

Benzoylphenylureas demonstrate the ability to act in eggs development, with a reduction in hatching of eggs treated with novaluron in the species *Leptinotarsa decemlineata* Say (1824) (Coleoptera: Chrysomelidae), known as Colorado potato beetle (Alyokhin, et al., 2008), *Cydia pomonella* (Linnaeus, 1758) (Lepidoptera: Tortricidae), the codling moth (Kim, et al., 2011), and *Cronotrachelus nenuphar* (Herbst, 1906) (Coleoptera: Curculionidae), the plum curculio (Hoffmann, et al., 2008). Substances as diflubenzuron, teflubenzuron, chlorfluazuron, flufenoxuron and cyromazine have an ovicidal effect on the development of *Thrips palmi* Karny (1925) (Thysanoptera: Thripidae), commonly known as melon thrips (Kubota, 1989).

Larvicidal/ninficidal potential

The use of IGRs to control larvae, nymphs or pupae represents an important strategy to avoid an emergency in reproductively viable adults, affecting the density of insect crops characterized as agricultural pests. Many of these substances can develop toxicity activities when applied to insects at an early stage, affecting their hormone levels and development.

CSI can be analyzed as potential larvicides using different compounds, although it is not yet certain which method of application of these substances is the most effective. Peres-Farinos et al. (1998) expressed the capacity of benzoylphenylureas to have greater toxicity through an oral application, compared to topical and continuous treatments. Studies like that of Bitsadze et al. (2013) reinforce the potential for oral applicability, where the treatment of second instar insects of *L. migratoria* fed with treated maize leaves demonstrated mortality; as well as the reports of Hosseinzadeh & Delkhoom (2013) who, analyzing the development of *L. decemlineata* in potato leaves treatments with CSI, showed a toxicity in second instar larvae. On the other hand, Kubota (1989) used treatments of different types of CSI in *T. palmi* and chose substances such as chlorfluazuron and flufenoxuron as potential ninficides in melon infestations control, corroborating the applicability of techniques that are based on continuous treatment. Observations of Joseph (2017) with *Bagrada hilaris* (Burmeister, 1835) (Hemiptera: Pentatomidae), the Bagrada bug, demonstrated a potential applicability for topical treatment of novaluron and diflubenzuron and lethality levels in nymphs.

Among benzoylphenylureas with larvicidal/ninficidal activity, studies with hexaflumuron can be grouped in *Ephestia figulilella* (Gregson, 1871) (Lepidoptera: Pyralidae), a moth known as a grape pest; *Spodoptera exigua* (Hubner, 1808) (Lepidoptera: Noctuidae), the beet armyworm; *Plutella xylostella* (Linnaeus, 1758) (Lepidoptera: Plutellidae), known as the diamondback moth; *Aphis craccivora* Koch (1854) (Hemiptera: Aphididae), the cowpea aphid; *Aubeonymus mariaefranciscae* (Roudier, 1981) (Coleoptera: Curculionidae), a beet pest; and *Ceroplastes floridensis* Comstock (1881) (Hemiptera: Coccidae), known as the Florida wax scale (Eisa, et al., 1991; Perez-Farinos, et al., 1998; Khajepour, et al., 2012; Li, et al., 2014). Diflubenzuron has shown effects on *S. littoralis*; *Heliothis virescens* (Fabricius, 1781) (Lepidoptera: Noctuidae), known as the tobacco budworm; *T. palmi*; *L. migratoria* and *B. hilaris* (Guyer & Neumann, 1988; Kubota, 1989; Bitsadze, et al., 2013; Joseph, 2017). Treatments with lufenuron culminated in mortality of *Lobesia brotana* (Denis & Schiffermuller, 1775) (Lepidoptera: Tortricidae), the European grapevine moth; *E. figulilella*; *Oxycarenus hyalinipennis* (Costa, 1847) (Hemiptera: Lygaeidae), a cotton pest; and *L. decemlineata* (Pavan, et al., 2005; Khajepour, et al., 2012; Hosseinzadeh & Delkhoom, 2013; Atta, et al., 2015). The activity of the insecticide flufenoxuron was evaluated in *L. brotana* and *T. palmi* (Kubota, 1989; Pavan, et al., 2005). Guyer & Neumann (1988), when analyzed the effects of CSI in *S. littoralis* and *H. virescens*, reported a greater toxicity of chlorfluazuron compared to diflubenzuron; and the same type of chlorfluazuron larvicidal potential was observed by Kubota (1989) in *T. palmi*. Etoxazole obtained a greater insecticidal activity in larvae of *S. exigua*, *P. xylostella* and nymphs of *A. craccivora* than treatments with hexaflumuron and chlorfluazuron (Li, et al., 2014).

JH mimics demonstrate larvicidal/ninficidal activity in the insect orders Lepidoptera and Hemiptera. In lepidopterans, the substances methoprene, pyriproxyfen and fenoxycarb were tested *in S. littoralis* and *Spodoptera frugiperda* (J.E. Smith, 1797) (Lepidoptera: Noctuidae), the fall armyworm, with a result of greater toxicity to fenoxycarb in *S. littoralis* larvae (El-Sheik, et al., 2016). The effectiveness of fenoxycarb was also seen in treatments with *P. xylostella*, showing high toxicity in third instar larvae (Mahmoudvand & Moharramipour, 2015). In Hemiptera, the activities of a serie of compounds derived from p-(1,5-dimethylhexyl)benzoic acid in the genus *Dysdercus* were evaluated, showing a sensitivity for species belonging to the Pyrrhocoridae family commonly known as cotton stainer bugs, comprising *Dysdercus intermedius* (Distant, 1890), *Dysdercus discolor* Walker, *Dysdercus chaquensis* Freiberg (1947), *Dysdercus cingulatus* (Fabricius, 1775) and *Dysdercus superstitiosus* (Fabricius, 1775) (Suchy, et al., 1968). Eisa et al. (1991) used *C. floridensis* as a study model to analyze its development against JH analogues such as fenoxycarb, Pro-done, R-20458 and dofenapine, aiming at preventing the development of nymphs treated with fenoxycarb and dofenapine. Pyriproxyfen expressed lethality in *D. citri* nymphs, which was not observed in treatments with adults (Boina, et al., 2009).

S. littoralis was used as a model in studies with the ecdysteroid agonists methoxyfenozide and tebufenozide, showing potential for larvae control (Ishaaya, et al., 1995; Adel & Sehnal, 2000). Methoxyfenozide also demonstrated larvicidal activities in works with the species *S. frugiperda* (Zarate, et al., 2009); *Helicoverpa armigera* (Hubner, 1808) (Lepidoptera: Noctuidae), the cotton bollworm (Alavo, et al., 2011); and in Carlson et al. (2011) work, who made an analysis of its effects not only in *S. frugiperda*, but also *in S. exigua*, *Trichoplusia ni* (Hubner, 1803) (Lepidoptera: Noctuidae) [cabbage looper], *Ostrinia nubilalis* (Hubner, 1796) (Lepidoptera: Pyralidae) [European corn borer], *C. pomonella*, and *Helicoverpa zea* (Boddie, 1850) (Lepidoptera: Noctuidae) [corn earworm].

Azadirachtin and its derivative products may also show larvicidal activity in treatments with crop pests. Tests with *Melia azedarach* L. (Meliaceae) extracts and neem oil in *Phyllocnistis citrella* (Stainton, 1856) (Lepidoptera, Gracillariidae), the citrus leafminer, culminated in larvae population decrease (Mckenna, et al., 2013). Essays with *S. littoralis* have shown mortality levels relative to 95% of treated larvae (Martinez & Emden, 2001). According to Joseph (2017), azadirachtin represents a viable option to be used in the field to control *B. hilaris*, also showing results in *Aphis gossypii* Glover (1877) (Hemiptera: Aphididae), known as cotton aphid, consisting of a reduction of 80.65% of nymphs treated (Andrade, et al., 2013).

Hormonal antagonists can exert larvicidal and ninficidal activities. The ecdysteroid antagonists withanolides were observed in plant species of Solanaceae and tested in *Ceratitis capitata* Wiedemann (1824) (Diptera: Tephritidae), known as Mediterranean fruit fly. Salpichrolide B, isolated from *Salpichroa origanifolia* (Lam.) Bail, demonstrated 95% larvae mortality (Bado, et al., 2004), and withanolide E and 4-ß-hydroxywithanolide E, major compounds from extracts of *Physalis peruviana* L., caused significant mortality in treated larvae (Cirigliano, et al., 2008).

The anti-juvenoids precocenes I and II, when tested in *S. gregaria*, showed mortality less than 20%, even in the highest doses, and the effectiveness of precocene I (Chenevert, et al., 1980). Precocene I experiments in *E. integriceps* pointed a dose-dependent mortality in third instar nymphs (Amiri, et al., 2010). Kanakugiol, another chemical substance with JH antagonist activity, presented in a treatment 50% mortality of *Laodelphax striatellus* (Fallén, 1826) (Hemiptera: Delphacidae) nymphs, the small brown planthopper (Fang, et al., 2017).

Potential in reproductive modifications

Substances of IGR activity can exert modifications in mechanisms of insect reproduction, altering not only the reproductive system of males and females but also the fertility, oviposition and eggs hatching.

Ecdysteroid agonists showed responses in lepidopteran agricultural pests. Adel and Sehnal (2000), when analyzing the effects of methoxyfenozide in *S.littoralis*, reported that the insects that managed to escape the lethality developed in adults with reduced fertility, and a sterility linked to an accumulation of the compound in the body and penetration into the developing gonads. Effects on the reproductive system were also evidenced by Seth et al. (2004), when a treatment with tebufenozide in *Spodoptera litura* (Fabricius, 1775) (Lepidoptera: Noctuidae), also known as tobacco cutworm, resulted in decrease of reproductive potential of males through the reduction of testicular volume and sperm release. Other mechanisms may be associated by reduction in fertilization, which was speculated by Sun et al. (2003) who, in studies of methoxyfenozide and tebufenozide application in *C. pomonella*, pointed out the possibility of inhibition in vitelogenic synthesis agonists presented in the fatty body, a translocation of substances in the hemolymph or an absorption by ovary. Exceptions can occur and demonstrate that not all the action exerted by ecdysteroid agonists in fertilization of crop pests is negatively regulated; there are reports that methoxyfenozide has increased not only the fertility in *S. littoralis*, but also egg laying (Ishaaya, et al., 1995). Oviposition alteration and eggs hatching activities can also demonstrate differences in mode of action. While Seth et al. (2004) observed a reduction in egg laying and hatching of the lepidopteran *S. litura* treated with RH-5849, Wang and Sehnal (2002) indicated an influence of methoxyfenozide on vitelogenesis acceleration and shortening of the eggs gonadotropic cycle of the grasshopper *S. gregaria*.

Among antagonistic activities, the ecdysteroid antagonist cucurbitacin B caused fertility suppression in parental generation of *A. gossypii* and generated effects that influenced his F1 generation (Yousaf, et al., 2018). JH antagonists can stimulate fertility and eggs maturation, and these data are possible to be visualized in treatments of precocene I in *Myzus persicae* (Sulzer, 1776) (Hemiptera: Aphididae), known as green peach aphid (Ayyanath, et al., 2015); and in precocene II treatments in *S. gregaria* (Eid, et al., 1988). On the other hand, Amiri et al. (2010) demonstrated the effects of reduction in laying and hatching eggs of *E. integriceps* insects submitted to precocene I.

JH analogs expressed the ability to alter the fertility of agricultural pests. While the dofenapine treatment in *C. floridensis* caused inhibition on eggs hatching (Eisa, et al., 1991), substances such as pyriproxyfen and buprofezine generated transovarian effects in *Stephanitis pyrioides* (Scott, 1874) (Hemiptera: Tingidae), the Azalea lace bug (Joseph, 2019). Pyriproxyfen also showed activity in *S. litura*, reducing its egg laying (Xu, et al., 2015), and fenoxycarb influenced in fertility decrease of *P. xylostella* (Mahmoudvand & Moharramipour, 2015). The methyl farnesoate compound was evaluated in tests with the cotton bugs *Dysdercus cardinalis* (Gerstaecker, 1873) (Hemiptera: Pyrrhocoridae) and *Dysdercus fasciatus* (Signoret, 1861) (Hemiptera: Pyrrhocoridae), pointing out effects on copulatory capacity and adults sterilization (Bransby-Williams, 1971; Critchley & Campion, 1971).

Transovarian activities related to a low number of nymphs were also seen after the treatment of *S. pyrioides* adults with azadirachtin (Joseph, 2019). The same substance demonstrated in a treatment with *Chaetosiphon fragaefolli* (Crockerell, 1901) (Hemiptera: Aphididae), the strawberry aphid, 28% of reduction in fertility (Bernardi, et al., 2012).

Compounds that inhibit chitin synthesis have mechanisms for altering the reproductive system of treated insects. The evaluation of flucycloxuron on the development of *Dysdercus koenigii* (Fabricius, 1775) (Hemiptera: Pyrrhocoridae), another of the bugs commonly known as cotton stainers, showed effects of reduced fertility, disintegration of follicular epithelium, reduced number of oocytes and an vitelogenesis inhibition (Khan & Qamar, 2011; 2012). Tests with lufenuron presented a sperm reduction in males of *Anthonomus grandis* Boheman (1843) (Coleoptera: Curculionidae), the boll weevil, as well as ovarian changes in females (Costa, et al., 2017). The same compound was tested in *S. gregaria*, showing analyzes of ovarian and testicular disruption (Ghazawy, 2012). Tail et al. (2008) observed, in diflubenzuron treatment of *S. gregaria*, a reduction in eggs number per ootheca and, with the observed results, formulated a hypothesis about the treatment have reduced the ecdysteroids levels in hemolymph, reflecting in ovarian synthesis reduction due to alterations in follicular chambers.

Several CSI demonstrate other types of activity. Novaluron showed effects of reduction in egg viability in *L. decemlineata* (Alyokhin, et al., 2008), and in *C. pomonella* (Gokçe, et al., 2008; Kim, et al., 2011); as well as demonstrated transovarian effects in *B.hilaris* and *S. pyrioides* (Joseph, 2017; 2019). Flufenoxuron was able to reduce the fertility of *S. littoralis* (Bakr, et al., 2010). Hatching inhibition was visualized in hexaflumuron treatments in *A. mariaefranciscae* (Perez-Farinos, et al., 1998), and in teflubenzuron application in *C. floridensis* (Eisa, et al., 1991).

Morphological and anatomical modifications generated by IGRs treatments

Insecticides can often have sublethal effects that compromise the morphological and anatomical structures of insects. Many of the effects reported by IGR for abnormalities of treated insects are related to ecdysis failures and wing deformities, which can constitute mechanisms to block its locomotion, viability and longevity. According to Bransby-Williams (1971), malformations in developmental process can influence the dispersion and reproduction of insects.

Anti-juvenoids demonstrate an influence on wing development process and, according to Hardie et al. (1996), can affect morphogenic pathways of induction or inhibition. Aphids showed sensitivity to JH antagonists regarding alar development, and an inhibition in *M. persicae* was evaluated by treatment with precocene III (Hales & Mittler, 1981); an induction of a winged offspring for the treatment of precocene I and III in *Acyrthosiphon pisum* (Harris, 1776) (Hemiptera: Aphididae), known as pea aphid, and *Aphis fabae* Scopoli (1763) (Hemiptera: Aphididae), known as the black bean aphid (Hardie, 1986); and an induction and inhibition by 2,2-dimethyl chromene and 2,2-dimethyl chroman precocene derivatives treatment in *A. pisum* (Hardie, et al., 1996). Deformational aspects in wings were observed in Orthoptera, through precocene I treatment in *L. migratoria* (Pedersen, 1978). Precocene I demonstrates other types of deforming effects in treatments with crop pests, such as the appearance of a poorly developed ventral thoracic portion in *L. migratoria* (Pedersen, 1978); and the presence of *E. integriceps* insects with deformities in scutellum, wings, and presenting disproportionately small and narrow abdomen and stomach (Amiri, et al., 2010; Kafi-Farashah, et al., 2018). Precocene II treatment in *S. littoralis* caused the elongation of treated larvae, and deformations in pupae and adults (Khafagi & Hegazi, 1999). Other alteration activities proposed by precocenes are modifications in the sensory system due to a reduction in the number of sensillae and disturbances in antennae development (Triseleva, 2003), and changes in pigmentation of treated insects (Pedersen, 1978; Eid, et al., 1988).

Different types of deformations could be seen in treatments of JH analogues in insects belonging to Lepidoptera, Hemiptera and Orthoptera. Singh and Kumar (2011), in pyriproxyfen treatments on *Papilio demoleus* (Linnaeus, 1758) (Lepidoptera: Papilionidae), the lime swallowtail, observed effects that comprised an incomplete detachment of exuvia in ecdysis process, culminating in mortality, and the appearance of an old head capsule linked to the new in some larvae; as well as showing rectal prolapse in larvae, different degrees of melanization in pupae, and deformations in the wings, antennae and legs of adults. Studies of *S. litura* against pyriproxyfen and diofenolan demonstrated the presence of “larva-pupa mosaics”, that is, insects that had altered their development and that acquired both larva and pupa characteristics; in addition to pupae with mouthparts and appendages out of the chrysalis and adults with alterations in wings, legs and genitalia (Singh & Kumar, 2015). El-Sheik et al. (2016) also showed mosaic insects and deformed adults of *S. littoralis* and *S. frugiperda* when treated with methoprene, pyriproxyfen and fenoxycarb. Morphological modifications in head and body color alteration were observed in *L. migratoria* (Cotton & Anstee, 1991) and *D. citri* (Boina, et al., 2009) in tests with methoprene and pyriproxyfen, respectively. The compound methyl farnesoate dihydrochloride developed modifications in *Dysdercus fasciatus* (Signoret, 1861)

(Hemiptera: Pyrrhocoridae), another cotton stainer, as wings that would be longer than normal, and some insects that had antennae with an extra segment (Critchley & Campion, 1971).

Crop pest species belonging to Coleoptera, Orthoptera, Hemiptera, Lepidoptera and Diptera demonstrated a series of abnormalities when treated with CSI insecticides. The beetle *L. decemlineata* was used as a model in different studies, showing common results such as being trapped in the old cuticle, hindgut protruding in a rectal prolapse and color change, consisting in treatments with the substances lufenuron, teflubenzuron, diflubenzuron, cyromazine, hexaflumuron and triflumuron (Karimzadeh, et al., 2007; Hosseinzadeh & Delkhoom, 2013; Meng, et al., 2018). Teflubenzuron had its activity evaluated in tests with *S. gregaria* carried out by Al-Mokhlef et al. (2012), who formulated a theory that the compound would destroy the integument cell structure and cuticle components and proved their hypothesis by results of ecdysis failures followed by death, and an 88.9% inhibition of chitin amount. Flucycloxuron showed abnormalities in *D. koenigii* as a shrunken abdomen, exuvia attached to the last abdominal segments and wrinkled wings (Khan & Qamar, 2011). Cuticular modifications, ecdysis failures, mosaic insects and color changes are results presented in treatments with lepidopterans, which can be observed in the study of flufenoxuron treatment in *S. littoralis* (Bakr, et al., 2010); in diflubenzuron treatment of *Pieris brassicae* (Linnaeus, 1758) (Lepidoptera: Pieridae), known as the large white butterfly (Gijswijt, et al., 1979); in the evaluation of the compounds chlorfluazuron and diflubenzuron in *S. littoralis* and *H. virescens* (Guyer & Neumann, 1988); in the use of hexaflumuron and lufenuron in *E. figulilella* (Khajepour, et al., 2012); and in the administration of the compounds diflubenzuron, PH 60-43, penfluron, PH 60-45, triflumuron, chlorfluazuron, teflubenzuron, XRD-473 and Dowco 439 in *Earias insulana* (Boisduval, 1833) (Lepidoptera: Noctuidae), the Egyptian stemborer (Meisner, et al., 1986). Chlorfluazuron, hexaflumuron, diflubenzuron and cyromazine tests in *Bradysia odoriphaga* (Yang & Zhang, 1985) (Diptera: Sciaridae), the chive gnat, showed abnormalities as darkened pupae, head and abdomen distension, wing dysplasia and ecdysis failures (Zhang, et al., 2016).

Azadirachtin presented, according to Bernardi et al. (2012), a color change in treated nymphs and mobility reduction, while Mordue and Nisbet (2000) pointed out abnormalities in molting processes of *S. gregaria* and *P. brassicae*. In *S. littoralis*, azadirachtin induced a series of changes such as ecdysis failures, cuticular formation failures, mosaic insects, and deformations in wings and mouthparts (Martinez & Emden, 2001).

Song et al. (2017) reported that activities commonly linked to ecdysteroid agonists are premature molting and incomplete ecdysis. This can be complemented by other studies, where Eizaguirre et al. (2007), when analyzing methoxyfenozide application in *Sesamia nonagrioides* (Lefébvre, 1827) (Lepidoptera: Noctuidae), known as the Mediterranean corn stalk borer, observed ecdysis failures and argued about the rapid process of molting does not allow a necessary time for larvae to transform in well-developed pupae; as well as in tebufenozide and bisphenol A tests in *S. nonagrioides* (Kontogiannatos, et al., 2014), and in tebufenozide and RH-5849 application in *S. litura* (Seth, et al., 2004). Other effects of methoxyfenozide were reported by Zarate et al. (2009) in *S. frugiperda*, where larvae treatment reduced not only the size of pupae and females, but also culminated in malformations of wings in adults.

Ecdysteroid antagonists demonstrate few evaluations of morphological changes in studies; however, the work of Bélai & Fekete (2003) serves as a source for this type of potential. In the study of *D. cingulatus* against azolic compounds, molting failures and insects attached to the old cuticle were reported, in addition to wing deformations that did not cover the entire abdomen. It has been speculated about the performance of 20-HE in wing morphogenesis control, influencing the alar deformations.

Alterations in developmental period

Certain IGRs have mechanisms that modify the insect developmental time, either by delaying the nymph/larva stages or by their prolongation, which constitutes control methods that prevent the appearance of adult insects.

The stimulation of molting and early metamorphosis is one of the activities already characteristic of precocenes, and its effectiveness is proven in the presence of early adults of *L. migratoria*, *S. gregaria*, *M. persicae*, *A. pisum* and *A. fabae* (Pedersen, 1978; Chenevert, et al., 1980; Hales & Mittler, 1981; Hardie, 1986; Eid, et al., 1988); and in early nymphs of *Nilaparvata lugens* (Stal, 1854) (Hemiptera: Delphacidae), the brown planthopper (Bertuso, et al., 2002).

Changes in developmental period are also observed in precocene treatments, showing results of delays in molting and metamorphosis (Chenevert, et al., 1980; Eid, et al., 1988), as well as in treatments with juvenoids and ecdysteroid agonists. Delays in ecdysis, larval prolongation and decreased pupation time were evidenced in pyriproxyfen applications in *P. demoleus*, and in pyriproxyfen and diophenolan use in *S. litura* (Singh & Kumar, 2011; 2015). Fenoxycarb demonstrated effects of larval and pupal prolongation on *P. xylostella* development (Mahmoudvand & Moharramipour, 2015). Ecdysteroid agonists also resulted in larval prolongation of *S. nonagrioides* (Kontogiannatos, et al., 2014), *S. littoralis* (Adel & Sehnal, 2000) and *S. frugiperda* (Zarate, et al., 2009).

Alterations in developmental stage

The ability of juvenoids to keep high the endogenous JH levels can guarantee an appearance of supernumerary nymphs, presenting characteristics of an adult insect, but which are not reproductively mature. In their studies, Singh and Kumar (2015) observed the appearance of adultoids on pyriproxyfen and diafenolan treatments in *S. litura*, corroborating the characterization of this type of potential in substances similar to JH. The methyl farnesoate dihydrochloride compound was able to stimulate the presence of supernumerary insects of *D. cardinalis* and *D. fasciatus* (Bransby-Williams, 1971; Critchley & Campion, 1971). However, the mechanisms that culminate the appearance of supernumerary nymphs have not yet been fully elucidated, and there may even be other compounds capable of inducing these transformations, taking as an example the presence of *E. figulilella* supernumerary nymphs in treatments with the CSI hexaflumuron and lufenuron (Khajepour, et al., 2012).

Fagoinhibition

Azadirachtin can be considered as one of the main substances studied in terms of the potential for altering insect feeding, integrating inhibitory and physiological processes. According to Mordue and Nisbet (2000), in low concentrations, azadirachtin is capable of expressing changes in chemoreceptors present in mouthparts, triggering a fagoinhibition that will culminate in starve of treated insects. Other compounds can exhibit the same type of activity, being distributed in almost all known classes of IGRs.

Adel and Sehnal (2000), in studies with *S. littoralis*, proved the effects of feeding prevention and death not only in treatments with azadirachtin, but also with the ecdysteroid agonist methoxyfenozide. Methoxyfenozide also demonstrates feeding interruption and weight reduction of *S. nonagrioides*, in addition to modifications in the digestive tract that restricted food intake (Eizaguirre, et al., 2007). Ascher et al. (1987) analyzed the activity of ecdysteroid antagonists such as withanolide E and 2,3-dihydrowithanolide E in *S. littoralis* and *Epilachna varivestis* (Mulsant, 1850) (Coleoptera: Coccinellidae), a pest known as the Mexican bean beetle, and linked the results obtained to a fago-repellency originating a reduction in the consumption of treated leaves or the toxicity exerted by the compounds. Tallamy et al. (1997) performed an analysis of cucurbitacin B activity on various agricultural pests, and came up with a hypothesis about the potential of fagoinhibition for mandibular species and a possible stimulating potential for sucking insects, being used *Popillia japonica* Newman, 1841 (Coleoptera: Scarabaeidae), known as the Japanese beetle; *Cerotoma trifurcata* (Foster) (Coleoptera: Chrysomelidae), the bean leaf beetle; *Trichoplusia ni* (Hubner, 1803) (Lepidoptera: Noctuidae), known as the cabbage looper; *Gargaphia solani* (Heidemann 1914) (Hemiptera: Tingidae), the eggplant lace bug; *Corythucha ciliata* (Say, 1832) (Hemiptera: Tingidae), the sycamore lace bug; *Peregrinus maidis* (Ashmead, 1890) (Hemiptera: Delphacidae), the corn delphacid, *Ostrinia nubilalis* (Hubner, 1796) (Lepidoptera: Pyralidae), the European corn borer; *S. exigua* and *A. pisum* as models of study.

The CSI teflubenzuron expressed a reduction in *L. decemlineata* larvae feeding (Meng, et al., 2018), as well as a brief fagoinhibition of *B. odoriphaga* insects treated with chlorfluazuron, hexaflumuron, diflubenzuron and cyromazine (Zhang, et al., 2016). The study of precocene activities showed, in *L. migratoria*, *M. persicae* and *Trialeurodes vaporariorum* (Westwood, 1856) (Hempitera: Aleyrodidae), known as the greenhouse whitefly, changes in excretory system that indicated a decline in feeding activity (Triseleva, 2003).

4. Conclusion

The review demonstrated the different types of potentials existing in IGRs regarding the control of insects considered crop pests. Hormonal deregulation mechanisms were presented, that culminate in the alteration of processes such as development, molting, metamorphosis and reproduction, which would allow a reduction in the density of insects and, consequently, in their economic losses. The knowledge gathered on the main pests used as study models and the main IGR compounds used permit an assessment of their use as a source of information for agricultural pest control methods. Further studies will be conducted to obtain a greater understanding of IGRs and their specific mechanisms of action in the development of insects considered pests.

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