A Review of *Nosema ceranae* and *Nosema apis*: Characterization and Impact for Beekeeping

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Abstract

Two microsporidia have been described infecting honey bees worldwide: *Nosema apis* and *Nosema ceranae*. The infecting forms of the parasite are the spores, ingested by the adult host insects. Studies demonstrated that the infection with *Nosema spp.* range from less than 1 to 100 percent, this disease reduces worker longevity by 22-44% which in turn reduces honey production and causes incomplete crop pollination. However, the used conventional drugs in beekeeping sector has a strong limitation due to the big concern about antibiotics resistance, transmission of antibiotics residues in beehive products and to a lesser extent, unbalancing risk of bee gut microbiota. This review highlights the importance to have healthy bee colonies, which implicitly lead to safety bee products. For this reason, orientation towards alternative treatments without antibiotics and based on natural products with higher antimicrobial effects it is very topical.

Keywords: *Apis mellifera*, nosemosis, bee products, treatments, beekeeping

Introduction

Nosemosis is one of the most serious diseases of adult honey bees occurring in nearly every country with beekeeping practices and it negatively decreases productivity and survival of honeybee colonies (Botias *et al.*, 2013; Huang, 2012), colony depopulation and collapse (Paxton, 2010) by affecting the development of the fat-protein body as well as the levels of proteins and fatty acids in the bee haemolymph (Chen *et al.*, 2009; Gajger *et al.* 2009), Nosemosis can reduce worker longevity by 22% to 44% (Kang *et al.*, 1976; Aydin *et al.*, 2006; Lotfi *et al.*, 2009), which in turn reduces honey production and causes incomplete crop pollination (Forsgren and Fries, 2003; Fries *et al.*, 2003). The infection has two

forms: the parasite multiply inside the cells of intestinal epithelium of honeybees (vegetative form) and another with a reduced metabolism usually it found in dead honeybees or when its eliminated in the outer environment (sporulated form) (Mărghitaș, 2017). and Based on molecular phylogenies, the microsporidia are included into the Opisthokonta rank, Fungi kingdom, Microsporidia phylum, *Dihaplophasea* class, *Dissociodihaplophasida* order, Nosematidae family, *Nosema* genus, *Nosema apis* and *Nosema ceranae* species. Microsporidia are, thus, to be regarded as highly specialized parasitic fungi (Sina *et al.*, 2005). *Nosema* contains more than 150 species, most of them infects invertebrate hosts (Higes *et al.*, 2007; Aurori *et al.*, 2011) causing some

well known diseases such as pebrine disease in silkworms (by *Nosema bombycis*) and dysentery in honeybees (by *Nosema apis*). In Romania, both species (*N. apis* and *N. ceranae*) exists in *Apis mellifera* colonies (Dumitru *et al.*, 2017).

The purpose of the present review is to describe the two bee parasitic forms: *N. apis* and *N. ceranae* and their impact for beekeeping. Also, the use of medicinal plants with therapeutic effects for prevent or treat nosemosis in bee colonies is described and encouraged.

Nosema apis* & *Nosema ceranae

The most common forms of *Nosema* spp in bees are: *Nosema apis* (Zander, 1909) and *Nosema ceranae* (Fries *et al.* 1996). *N. apis* is one of the first described microsporidian parasite and believed to be the only etiological agent of Nosemosis in the European honeybee (*Apis mellifera*) which can decrease worker longevity and cause considerable winter colony losses (Fries, 1993; Higes *et al.*, 2006; Williams *et al.*, 2008a; Szawarski *et al.*, 2019). The size of *N. apis* spores lies between 5-7 and 3-4 μm (Utuk *et al.*, 2016). Chioveanu *et al.* (2004) described the factors which determine the appearance of this disease, such as: the climate (the sudden variations of temperature, long and cold winters), the inappropriate hygiene of the beehive, some associated diseases such as amoebiasis and storage on winter period in the hive black color honey, rich in minerals, which may cause bee diarrhea.

Whilst *N. ceranae* originates from Asia and was originally described as a pathogen of the Asian cavity nesting bee *A. cerana* (Fries *et al.*, 1996) and it has been introduced into European honeybees within the last few decades (Higes *et al.*, 2006; Martín-Hernández *et al.*, 2007; Klee *et al.*, 2007; Paxton *et al.*, 2007; Chen *et al.*, 2008; Williams *et al.*, 2008a; Invernizzi *et al.*, 2009; Currie *et al.*, 2010; Botías *et al.*, 2011). Studies show that *N. ceranae* may be more virulent than *N. apis* when infecting *A. mellifera*, and colony depopulation and collapse in warmer areas of Europe, has been reported (Higes *et al.*, 2008a), but not in northern parts of Europe (Gisder *et al.*, 2010a), in North America (Guzman-Nova, 2010; Williams *et al.*, 2010a) or in South America (Invernizzi *et al.*, 2009). The spores of *N. ceranae* dimensions are between 4.4 x 2.2 μm (Utuk *et al.*, 2016).

The germination spores capacity and the Nosemosis multiplication depends essentially on temperature, i.e. 30°-35°C (*N. apis*), in winter and over 35°C (*N. ceranae*), during summer. *N. ceranae* spores can survive the frost, unlike *N. apis*.

Chemurot *et al.* (2017) describe a new microsporidian, *Nosema neumanni* n. sp., detected in some colonies in Uganda in addition to the known *N. apis* and *N. ceranae*. There are clear differences in the ultra-structural and molecular characteristics of the new mentioned *Nosema* specie, the spores are smaller under the TEM and the number of polar filament coils is between 10 and 12, compared to 20–23 for *N. ceranae* and more than 30 often seen in *N. apis* (Fries *et al.* 1996).

Interestingly, that some authors (Alaux *et al.*, 2010; Martin-Hernandez *et al.*, 2011; Vidau *et al.*, 2011) have described that *N. ceranae* can produce changes in the glucidic metabolism on honeybees. The explanations are that the infected worker appear to be unable to use the consumed excess of carbohydrates, because most of them are “forced” by the pathogen to complete its life cycle (Mayack and Nang, 2013).

Hence, the mechanisms controlling the mobilization of energy reserves appear to be disturbed and there is poor carbohydrate homeostasis in their haemolymph (Aliferis *et al.*, 2012). The stronger sugar demand and higher consumption could be a host response to the infection, directly related to the dependence of microsporidia on host energy. However, the intestinal lesions caused by *N. ceranae* proliferation may decrease the digestive capacity of honey bees and generate signs of starvation, such as impoverishment of hypopharyngeal protein secretions in nurse bees (Vidau *et al.*, 2014).

Additionally, Li *et al.* (2018) reported that bees infected by *N. ceranae* show an accelerated lipid loss, suggesting lipids that may be used also as a fuel for increased metabolic demands due to the infections.

Today Nosemosis is a worldwide disease present in every beekeeping country (Table 1.), although according to the OIE statistics, the parasite is spread in 43% of the countries having bee colonies. Thus, Table 1. represent the spreading of *Nosema* spp. infection worldwide, based on molecular analysis by the quoted authors.

Table. 1. *Nosema* spp. incidence infection in honey bee populations worldwide reported in scientific publications

Host	Year	Region and/or Country	<i>Nosema</i> species	References
Asia				
<i>A. ceranae</i>	1996	China	<i>N. ceranae</i>	Fries <i>et al.</i> , 1996
<i>A. ceranae</i> , <i>A. mellifera</i>	1992, 2007-2008	China, Japan, Taiwan	<i>N. ceranae</i> , <i>N. apis</i>	Chen <i>et al.</i> , 2009
<i>A. mellifera</i>	2009	Japan	<i>N. ceranae</i>	Yoshiyama and Kimura, 2011
<i>A. mellifera</i>	n.a.	Jordan	<i>N. ceranae</i>	Haddad, 2014
<i>A. mellifera</i>	2017	Saudi Arabia	<i>Nosema</i> spp.	Ansari <i>et al.</i> , 2017
<i>A. ceranae</i> , <i>A. mellifera</i>	2006	Vietnam	<i>N. ceranae</i>	Klee <i>et al.</i> , 2007
<i>A. ceranae</i> , <i>A. mellifera</i>	2008-2009	Thailand	<i>N. ceranae</i>	Chaimanee <i>et al.</i> , 2010
<i>A. mellifera</i>	2005-2006	Turkey	<i>N. apis</i>	Whitaker <i>et al.</i> , 2011
	2007-2009	Turkey	<i>N. ceranae</i>	Muz <i>et al.</i> , 2010
Northern Europe				
<i>A. mellifera</i>	1988-2006	Denmark	<i>N. apis</i> , <i>N. ceranae</i>	Klee <i>et al.</i> , 2007
<i>A. mellifera</i>	1986-1995	Finland	<i>N. apis</i>	Paxton <i>et al.</i> , 2007
	1998, 2002, 2006	Finland	<i>N. apis</i> , <i>N. ceranae</i>	Paxton <i>et al.</i> , 2007
	2006	Finland	<i>N. ceranae</i>	Klee <i>et al.</i> , 2007
	1998, 2003, 2005	Sweden	<i>N. apis</i>	Klee <i>et al.</i> , 2007
<i>A. mellifera</i>	2006	Sweden	<i>N. apis</i> , <i>N. ceranae</i>	Klee <i>et al.</i> , 2007
	n.a.	Sweden	<i>Nosema</i> spp.	Fries, 2010
<i>A. mellifera</i>	2011-2014	Lithuania	<i>N. ceranae</i> , <i>N. apis</i>	Blazyte-Cereskiene <i>et al.</i> , 2016
Eastern Europe				
<i>A. mellifera</i>	2014-2016	Ukraine	<i>N. apis</i> , <i>N. ceranae</i>	Odnosum, 2017
Central Europe				
<i>A. mellifera</i>	2003, 2005-2006	Germany	<i>N. ceranae</i> , <i>N. apis</i>	Martin-Hernandez <i>et al.</i> , 2007; Klee <i>et al.</i> , 2007
	2005-2016	Germany	<i>N. ceranae</i> , <i>N. apis</i>	Gisder <i>et al.</i> , 2017
<i>A. mellifera</i>	1994	Hungary	<i>N. apis</i>	Klee <i>et al.</i> , 2007
	2006-2007	Hungary	<i>N. ceranae</i> , <i>N. apis</i>	Tapasztai <i>et al.</i> , 2009
	2017	Hungary	<i>Nosema</i> spp.	Şapcaliu <i>et al.</i> , 2017
<i>A. mellifera</i>	2006	Switzerland	<i>N. ceranae</i> , <i>N. apis</i>	Martin-Hernandez <i>et al.</i> , 2007
	2011	Switzerland	<i>N. ceranae</i>	Tritschler <i>et al.</i> , 2017
Western Europe				
<i>A. mellifera</i>	2002-2005	France	<i>N. ceranae</i> , <i>N. apis</i>	Chauzat <i>et al.</i> , 2007
	2006	France	<i>N. ceranae</i> , <i>N. apis</i>	Martin-Hernandez <i>et al.</i> , 2007

<i>A. mellifera</i>	2005	Ireland	<i>N. apis</i>	Klee et al., 2007
<i>A. mellifera</i>	2007-n.a.	England	<i>N. apis</i> , <i>N. ceranae</i>	Budge, 2008
<i>A. mellifera</i>	2001, 2005-2006	UK (Northern Ireland)	<i>N. apis</i>	Klee et al., 2007
Southeastern Europe				
<i>A. mellifera</i>	2006-2009	Fyrom	<i>N. ceranae</i>	Stevanovic et al., 2011
<i>A. mellifera</i>	2006-2009	Bosnia and Herzegovina	<i>N. ceranae</i>	Stevanovic et al., 2011
<i>A. mellifera</i>	2017	Bulgaria	<i>N. ceranae</i>	Shumakova et al., 2018
<i>A. mellifera</i>	2006-2009	Montenegro	<i>N. ceranae</i>	Stevanovic et al., 2011
<i>A. mellifera</i>	2015	Romania	<i>N. ceranae</i>	Mederle et al., 2018
<i>A. mellifera</i>	2006	Serbia	<i>N. ceranae</i>	Klee et al., 2007
	2000-2005, 2006-2009	Serbia	<i>N. ceranae</i>	Stevanovic et al., 2011
Southern Europe				
<i>A. mellifera</i>	2005-2006	Greece	<i>N. ceranae</i>	Klee et al., 2007
<i>A. mellifera</i>	1993, 1998, 2010	Italy	<i>N. ceranae</i> , <i>N. apis</i>	Ferroglio et al., 2013
	1994	Italy	<i>N. apis</i>	Klee et al., 2007
	2005-2006	Italy	<i>N. ceranae</i>	Klee et al., 2007
	2014-2015	Italy	<i>N. ceranae</i>	Papini et al., 2017
<i>A. mellifera</i>	2004-2005, 2005-2006	Spain	<i>N. apis</i> , <i>N. ceranae</i>	Higes et al., 2006; Martin-Hernandez et al., 2007; Klee et al., 2007
North America				
<i>A. mellifera</i>	2008, 2010, 2012	Canada	<i>N. ceranae</i> , <i>N. apis</i>	Emsen et al., 2016
<i>A. mellifera</i>	2006-2007	Maritime Provinces of Canada and Minnesota	<i>Nosema spp.</i>	Williams et al., 2008a
<i>A. mellifera</i>	1995-2007	USA	<i>N. ceranae</i>	Chen et al., 2008; Klee et al., 2007
	2009	USA	<i>Nosema spp.</i>	Traver and Fell, 2011
South America				
<i>A. mellifera</i>	2006	Brazil	<i>N. ceranae</i>	Klee et al., 2007
	2009-2012	Brazil	<i>Nosema spp.</i>	Teixeira et al., 2013
<i>A. mellifera</i>	2010-2012	Chile	<i>N. ceranae</i>	Martinez et al., 2012
<i>A. mellifera</i>	1995-1996	Mexico	<i>N. ceranae</i>	Guerrero-Molina et al., 2016
<i>A. mellifera</i>	1990, 2004, 2007-2008	Uruguay	<i>N. ceranae</i>	Invernizzi et al., 2009
Africa				
<i>A. mellifera</i>	2014-2015	Uganda	<i>N. ceranae</i> , <i>N. apis</i> , <i>N. neumannii</i>	Chemurot et al., 2017
Oceania				
<i>A. mellifera</i>	2007-2008	Australia	<i>N. apis</i> , <i>N. ceranae</i>	Giersh et al., 2009
<i>A. mellifera</i>	2006	New Zealand	<i>N. ceranae</i> , <i>N. apis</i>	Klee et al., 2007

How is *Nosema* spp. transmitted?

Nosema is transmitted through the ingestion of spores via contaminated water or food, through the exchange of food between bees or when they perform their cleaning duties (Ptaszyńska *et al.*, 2012; Martin-Hernandez *et al.*, 2018; Odemer *et al.*, 2018). Nosemosis infections are transmitted horizontally among bees, by ingestion of spores from the environment. For example, housecleaning bees, on removing nosema-infected bee feces deposited in the hive, material with infective spores, from infected worker honeybees. Thus, trophallaxis may be an important transmission pathway from bee to bee, or from colony to colony, because infected bees can contaminate beekeeping material when they are crushed during hive manipulation (Higes *et al.*, 2010). Moreover, queens commerce and their worker bee escorts may be a source of infection when they comes from another geographic area (Giersch *et al.*, 2009).

Bee pollen stored in honeycombs is a reservoir of *N. ceranae* spores from the self-contamination during the process of pollen collection (regurgitation, saliva etc.) (Higes *et al.*, 2010).

The median infective dose for *N. apis* has been described to be 94.3 spores per bee (Fries, 1988) whereas for *N. ceranae* it was established in 149 spores per bee, although the minimum dose capable of causing a detectable infection was 1.28 spores (McGowan *et al.*, 2016). The *Nosema* infection cycle is well understood. Spores are ingested by the honeybees and germinate quickly in the midgut (Odemer *et al.*, 2018). The spores extrude the polar tube and penetrates in the epithelial cells to release the sporoplasm directly into the cytoplasm (Higes *et al.*, 2007; Fries, 2010). Within a week, the host epithelial cells are filled with offspring spores (Graaf *et al.*, 1994; Gisder *et al.*, 2011) and the cells can burst to release a new generation of primary spores. If the honeybees can block the further infection, the primary spores develop into environmental spores and excreted through the feces. Otherwise, primary spores will germinate again and keep infecting more cells. However, the mechanisms of blocking *Nosema* infection in honey bees are still unclear (Huang *et al.*, 2012).

Bee products

Bee products are multicomponent natural substances necessary for the proper course of

basic life reactions (Bobiş *et al.*, 2010). These include the following: honey, bee pollen, and extracts derived from it, that is, bee bread, propolis, royal jelly, and bee venom (Basim *et al.*, 2006; Mărghițaș, 2017). Bee products demonstrated a wide range of healing effects. They increase the level of ATP, thus neutralize an effect of many toxic agents, increase immunity of an organism, and improve the energy balance of tissues (Kieliszek *et al.*, 2018). Today, consumer interest regarding honey and its derived products is oriented towards organic foods, and if antibiotics are used in bee colonies (like Fumagillin B), which is the only treatment available now on the market that can be used to treat nosemosis, although its effectiveness is questionable as it is not effective on the mature spores of *Nosema*, then this antibiotic can be found in the bee product. Without alternative treatments for *Nosema*, organic beekeepers will struggle to produce organic bee products, with high losses of the untreated hives. Regarding this, the European Commission establishes that the qualification of organic honey and other bee products as being from organic production is closely bound to the characteristics of hive treatments as well as the quality of the environment (Chiesa *et al.*, 2016). This qualification also depends on the conditions of extraction, processing and storage of bee products. The Council Regulation 1804/1999 EC is very restrictive with regard to the production of organic honey in terms of the origin of bees, siting of the apiaries, feed, disease prevention and veterinary treatments.

Impact of beekeeping practices

The importance of beekeeping is due, on one hand, to the nutritional and therapeutic value of the products obtained from the practice of this activity (honey, bee pollen, propolis, royal jelly and bee venom), and on the other hand, to the pollination services, because approximately 80% of the crops are pollinated by bees (Dirina and Bugina, 2012).

The *Nosema* parasite is ubiquitous, in temperate conditions, Nosemosis being considered to have a serious negative effect on the production capacity of honeybees colonies and the survival capacity of the affected colonies during the winter (Mitrea, 2011; Dumitru *et al.*, 2017).

One of the goals of modern beekeeping is to obtain residue-free bee products, as well as a revival of researches related to using natural products for

treatment in different pathological conditions. Botias *et al.* (2012b) and Simeunovic *et al.* (2014) showed the important role of the queen's age for the bee colonies and they suggested to replace an old queen by a younger one, for decrease the proportion of *Nosema* infection in the hive. It was also recently shown that the therapeutic doses of oxalic acid used for *Varroa* control might inhibit the development of *N. ceranae* in laboratory and field conditions, both at the individual and colony levels (Nanetti *et al.*, 2015). There is also some evidence that formic acid fumigation may help to suppress *Nosema* (Underwood and Currie, 2009). Moreover, Costa *et al.* (2010) reported that thymol and coumaphos used against *Varroa* can be suspected to increase susceptibility to infection by *N. ceranae*.

Over the years of confronting nosemosis, much effort has been invested in searching effective cure against this. So far, bicyclohexylammonium fumagillin, an antibiotic isolated from the fungus *Aspergillus fumigatus*, is one of the few drugs known to be active against microsporidia (McCowen *et al.*, 1951), suppressing their reproduction and multiplication at recommended concentrations (Higes *et al.*, 2011; Huang *et al.*, 2013).

Fumagillin is extensively used to control *Nosema* disease in apiculture for over 60 years and inhibits the enzyme methionine aminopeptidase-2 (MetAP2) activity (Martín-Hernández *et al.*, 2012). In the commercial formulation, fumagillin is present as a salt in an equimolar quantity with dicyclohexylamine (DCH).

Mutinelli (2003) described a protocol for the application of fumagillin against *Nosema apis*. This protocol assume a mix 100 mg of fumagillin to 1 gallon of sugar syrup (mix 2 parts sugar to 1 part water). Unfortunately, the toxicity of fumagillin can cause different illness for humans due to the remanence of residues in hive products (van den Heever *et al.*, 2014). For this reason fumagillin is no longer available on the EU market since January 1st, 2000 (van den Heever *et al.*, 2016a). Also, the fumagillin treatment is prohibited in US and Israel during the foraging season and it is commonly prophylactically applied to the hives in late fall and early spring in most of the US and Canada (Huang *et al.*, 2013; Williams *et al.*, 2011) or in November-December in Israel.

It has also been reported that *N. ceranae* seems to reproduce even better at lower concentrations of

fumagillin, which also affects the bees' physiology, such that its use may augment the prevalence of *N. ceranae* (Huang *et al.*, 2013). Risks related to the use of antibiotics for the control of honeybee diseases are persistence of the infection, reappearance of the disease and honey contamination (Directive 86/23/CE and further amendments)

Several semisynthetic and synthetic fumagillin analogues were shown to possess biological activity against *N. ceranae* under laboratory conditions but none were as effective as Fumagillin-BVR (van den Heever *et al.*, 2016a). Finally, a promising assay has shown that the administration of autoclaved spores to larvae was able to reduce the infection levels of adults by 57% without significantly altering larval or adult longevity (Endler, 2014).

Natural products

However, current trends offer great importance to the antimicrobial effects that some natural products can have on bee colonies (Table 2.). The most popular alternative treatments against nosemosis in Europe are Api Herb, Nozevit, Vita Feed Gold, Protofil, Hive Alive and Nosestat. Gajger *et al.* (2009) has demonstrated Nozevit treatment in comparison with non-treated bee colonies, a considerable reduction in spores: 48.73% on 10th day; 50.46% on 15th day and 70.91% on 22nd day after artificial infection with *N. apis* spores. Another study on nutraceutical, prebiotic and probiotics showed that acacia gum as the most effective prebiotic, although had a high mortality as side effect, and the probiotic Protexin Concentrate VC single-strain (Protexin C1) as able to reduce the spores, increasing the bee survival (Borges, 2015).

In Romania, Chioveanu *et al.* (2004) has tested the efficacy of Protofil in two apiaries between 1999-2002 and as after 10 series of administration, the therapeutic effect of the medicine assessed on the basis of the laboratory exam was: apiary I – 74% and apiary II -89%. Dumitru *et al.* (2017) have tested a mixture of medicinal herbs and etheric oils obtained from melliferous plants against Nosemosis and verified the toxicological effects for honeybees.

Ptaszyńska *et al.* (2017) demonstrated that the PP(Asp)2 don't have adverse effects on honeybee lifespan and the introduction of PP(Asp)2 into the diet of nosemosis-infected honeybees resulted in significant reduction ($F = 19.212$ and $p = 0.022$ on day 12) in the number of *Nosema* spores, for

Table. 2. Natural products effectiveness used in preventing or treating *Nosema spp.*

Natural products	<i>N.apis</i>	<i>N.ceranae</i>	References
<i>Artemisia absinthium</i> L. extract	X		Pohorecka, 2004
Protofil	X		Chioveanu <i>et al.</i> , 2006
Natural Essential Oils	X	X	Dumitru <i>et al.</i> , 2017
Propolis extract		X	Suwannapong <i>et al.</i> , 2018
Commercial probiotics and prebiotics		X	Ptaszyńska <i>et al.</i> , 2016
Nozevit	X		Gajger <i>et al.</i> , 2009
TMePyP and PP(Asp)2 Porphyrins		X	Ptaszyńska <i>et al.</i> , 2017
Laurel, Origanum, Rosemary, Cinnamon and Eucalypt essential oils		X	Porrini <i>et al.</i> , 2017

this reason we consider that the prophyrins are promising alternatives to conventional antibiotics.

Conclusion

The sudden changes of the temperature, late spring, raining autumn, bad food, matures of aged bees are a few factors which can induce the Nosemosis in the apiary, therefore the present study intends to contribute to highlight the importance of implementing prevention, treatment and control measures of honeybees Nosemosis and using the natural products based on medicinal plants. Modern trends concerning consumer's behavior and needs set the directions for the development of new products and thus new technology for their production. In this conditions of an organic beekeeping, natural products based on plant extracts can be an alternative to control of honeybees' diseases; by using of these products can be also avoided risks of drug residues in apiculture products.

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