The tapeworm *Ligula intestinalis* (Cestoda: Pseudophyllidea) inhibits LH expression and puberty in its teleost host, *Rutilus rutilus*

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Abstract

The tapeworm *Ligula intestinalis* occurs in the body cavity of its cyprinid second intermediate host, in this study the roach *Rutilus rutilus*, and inhibits host gonadal development. The mechanism by which infected fish are prevented from reproducing is unknown. Comparison of parameters, such as body length and weight, and condition factor and age, between infected and uninfected individuals, indicated only minor effects of parasitism on growth and condition. In contrast, seasonal gonadal development, as observed in uninfected fish, did not occur in infected fish, and gonads remained small and blocked at the primary oocyte stage in female roach. As immature ovaries and testes are still present, the parasite is presumed to act upon the brain–pituitary–gonadal axis of the fish to inhibit further development of reproductive organs. We investigated the *Ligula*/*fish* interaction at the level of the pituitary gland by determination of gonadotrophin (LH) content using a heterologous RIA for carp (*Cyprinus carpio*) LHβ subunit. The results indicated that the pituitary glands of infected roach contained approximately 50% less LH than non-infected fish. After the cloning and sequencing of roach LHβ subunit, we measured roach LHβ mRNA levels by real-time RT-PCR. A corresponding 50% reduction in LHβ mRNA pituitary levels was determined. These results reflect a significant and measurable effect of parasitism on the pituitary gland, and lend support to the hypothesis that excretory/secretory products released from the parasite interact with the brain–pituitary–gonadal axis of the fish host and thus inhibit gonadal development.

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Introduction

Previous studies have revealed that several parasitic infections can affect host reproduction. For example, Joose & van Elk (1986) noted that *Trichobilharzia ocellata* induces gigantism and the cessation of egg production in its molluscan host, a snail *Lymnea stagnalis*, and Crews & Yoshino (1989) observed that *Schistosoma mansoni* similarly suppresses reproduction and gonadal growth in another snail species, * Biomphalaria glabrata*. Furthermore, in vertebrate hosts, *Taenia taeniaeformis* appears to directly affect the testis in the rat (Lin et al. 1990) and *Taenia crassiceps* induces feminisation in infected mice (Larralde et al. 1995).

*Ligula intestinalis*, which is found in the body cavity of certain cyprinid fish, inhibits reproduction in both male and female fish. The gonads, however, are present but remain in an immature state, irrespective of fish age or season. Although this phenomenon has been reported several times (e.g. Arme & Owen 1968, Mahon 1976, Sweeting 1977, Bean & Winfield 1989), the mechanism of the action of this parasite remains unknown. Previous studies have indicated effects of infection at the pituitary gland level. Kerr (1948) and Arme (1968) noted that in ligulosed roach, *Rutilus rutilus*, the putative gonadotrophs are much reduced in number, compared with non-ligulosed individuals, are only lightly granulated, and have an irregular nuclear membrane, no prominent nucleolus and a marked reduction in the cytoplasmic volume. These studies have led to the belief that the effects of *Ligula* on gonadal development may be mediated through the pituitary gland. The effects noted in the wild are reproducible with a small plerocercoid implanted into a large mature fish, which precludes pressure effects on fish organs or general debilitation from parasite metabolic demands (Arme 1968, 1975). In addition, analogous effects have been shown
when *L. intestinalis* was implanted into the African clawed frog, *Xenopus leavis*, suggesting a general endocrine effect (Arme 1968).

In this study, our objective was to establish whether gonadal inhibition induced by *Ligula* in its primary fish host, *Rutilus rutilus*, is mediated through effects on pituitary gland hormone levels, i.e. teleost gonadotrophin hormone IIβ (homologous to tetrapod luteinizing hormone (LH)), as one of several key regulators of reproductive development within the pituitary–gonadal axis.

**Materials and methods**

**Fish**

Ligulosed and non-ligulosed roach were collected from the Altami Angling Club, Chester, Cheshire, UK during 2000–2001 at three times during the reproductive year: February (leading up to spawning in spring), August (post spawning) and December (mid cycle). Fish used for hormonal or molecular biological analysis were examined within 7 days of capture. Roach were maintained in Keele University aquarium in aerated, dechlorinated tap water at 14–18°C and fed on commercial fish meal (Aquatic 3e, Mazuri Zoo Foods, Essex, UK).

**Biometric parameters, age, parasitism**

All fish were anaesthetised in 2-phenoxy-ethanol (1 ml/l). Measurements of length, weight, age and parasite burden were recorded, and Fulton’s condition factor (K) was determined (K = 100 × body weight minus the gonad weight/body length³, expressed in g and cm respectively). Fish age was obtained from scale annuli, as advised by the National Fish Ageing Laboratory, Environment Agency, Brampton, Cambridgeshire, UK. The parasitisation index (PI) (% PI = (parasite weight/fish weight minus parasite weight) × 100) was established in infected individuals.

**Gonads**

The gonadal somatic index (GSI) (% GSI = (gonad weight/fish weight) × 100) was determined in non-ligulosed fish only. Since gender determination is very difficult in infected fish because of the small size of the gonads, the mid-section of infected fish was fixed in 10% buffered formalin and processed for histological determination of sex. A subset of four non-infected female fish from each group was used for histological analysis of gonadal development and two categories of oocytes were observed, i.e. primary oocytes and vitellogenic oocytes. With vitellogenic oocytes, the diameter of each egg and its corresponding yolk component in three successive sections was recorded and the largest yolk diameter used to determine the oocyte volume (volume = 4/3 πr³, n = 50 oocytes for each fish).

**RIA of pituitary LH**

Pituitary glands were collected individually from infected and non-infected fish, immediately frozen in liquid nitrogen and stored at −80°C. Individual pituitary gonadotrophin levels were determined for infected and non-infected roach by a heterologous RIA for carp (*Cyprinus carpio*) LHβ subunit (as described by Burzawa-Gerard & Kerdelhue 1978). Each pituitary gland was sonicated in 500 µl 0.6% NaCl and a 20 µl sample was assayed in triplicate.

**Cloning and sequencing of pituitary LH and 18S rRNA**

Because of the lack of sequence data available for roach, fragments of LH and the control gene 18S ribosomal RNA were amplified and sequenced to identify specific primers for use in real-time PCR. Complementary DNA was generated from a total RNA extraction (TRlzol; Life Technologies) of 30 mature roach pituitary glands. Degenerate primers were designed through global alignment (CLUS-TALW tool of DNASTar Inc., Madison, USA) of highly conserved regions of LH and 18S rRNA from other teleost species found in GenBank (e.g. common carp, *Cyprinus carpio*; goldfish, *Carassius auratus*; European eel, *Anguilla anguilla*). Reverse transcription of total RNA was performed using 5 µg RNA, random primers and SuperScript reverse transcriptase (Invitrogen). A touchdown amplification protocol was used involving a 10-min hot start at 95°C, five cycles of decreasing annealing temperatures from 55, 50, 45 to 40°C, followed by 25 cycles at 37°C. Denaturation was performed at 95°C for 15 s, annealing for 30 s and primer extension at 72°C for 1 min at each cycle after the initial denaturation step. The following degenerate primers were used: 5′-gARAARgAlgFTGYCCI-AMRTg-3′ and 5′-CATIKTRCAAIARISWRCARTCRA-3′. The amplified fragment was extended using rapid amplification of cDNA ends (5′ and 3′ RACE) using cDNA prepared with the SMART RACE kit (Clontech, BD Biosciences, Palo Alto, CA, USA) as a template and primers derived from the sequence of the initial fragment. The gene-specific primer used for 5′RACE was 5′-gGCCgTTCCT-CACTgCTACCAA-3′ and 5′-TTggTAACgATCggTggA-gAACgggCT-3′ for 3′RACE. For 18S rRNA, the degenerate primers 5′-CCACgggTAAgCggATACgg-3′ and 5′-gACDMggggCCgCRKAACTA-3′ were designed. PCR and RACE products were ligated into TOPO TA 2.1 cloning vector (Invitrogen). The nucleotide sequences of cloned DNA inserts were sequenced on an automated sequencer (ABI Prism 377; Applied Biosystems, Courtaboeuf, France) from 750 ng material.

**Measurement of LH mRNA levels by real-time PCR**

Total RNA was extracted from pools of three roach pituitary glands using the TRlzol method. RNA samples were resuspended in 20 µl nuclease-free water and treated for the removal of contaminating DNA using DNase I (Promega)
as previously described (Sambrook & Russell 2001) and stored at –80°C. Reverse transcription was performed on 2 µg total RNA per sample using ThermoScript RT (Invitrogen) with random hexamer primers (Invitrogen) in a final volume of 25 µl according to the manufacturer's instructions. Aliquots of the RT reaction corresponding to 50 ng reverse transcribed RNA served as a template for each triplicate 50 µl PCR reaction. Oligonucleotide primer sequences for LH and 18S rRNA were obtained using the Primer Express software (Applied Biosystems) from partial gene fragments acquired as described above. For LH, a 51 bp product was amplified with 5'-AgTCggAggTTCgAAgACgAT-3' and 5'-TCgTAgTTCCgACCgTAAACg-3'. As an internal control, 18S rRNA was amplified in an identical manner. Specific primers of 5'-TgCTTgACgAAgACCTgTA-3' and 5'-TTCTCCACTgTCTACCAACACT-3' produced a 56 bp amplicon. Data were analysed using the ABI Prism 7000 sequence detection system (Applied Biosystems). Transcript levels were normalised to those of 18S rRNA and data for infected fish presented as a fold change relative to the values obtained for non-infected fish.

**Statistical evaluation**

All results are expressed as means ± S.E.M. Statistical comparisons were made using the Student's t-test for analysis of infected and uninfected LH pituitary content. For real-time RT-PCR, a fully nested one-way ANOVA followed by a Tukey–Kramer multiple comparisons test was employed and the data were checked for normality. Correlations between body parameters were subjected to regression analysis. Differences were considered significant at $P < 0.05$.

**Results**

**Parasite burden**

Details of fish used and effects of parasitism are shown in Table 1. The PI encountered in this study parallels that noted in other investigations (Arme & Owen 1968, Sweeting 1977) with a PI which varied from 2.56 to 43.66% (mean 18.93 ± 1.3%). While roach were caught up to 54 g in weight, fish exceeding 20 g were not infected with Ligula (Fig. 1). In addition, in the 2000–2001 cohort examined, infection was detected throughout the age classes recorded (2–5 years), although parasitisation was more frequent in the lower age groups (88% for age classes 2+ and 3+ year-old fish, 12% for 3+ and 4+ year-old fish). The PI did not increase significantly with the age of the fish (ANOVA, $F = 0.32, P > 0.05$).

**Effects of parasitism on host: body growth and condition**

A significant difference ($T = 4.03, P < 0.05$) was observed between the mean length of ligulosed fish (79.8 ± 2.1 mm) when compared with non-ligulosed individuals.

**Table 1** Data summary for all experimental fish. Figures given are means ± range.

<table>
<thead>
<tr>
<th>Collection date and number</th>
<th>Average age (years)</th>
<th>Average length (mm)</th>
<th>Average weight (g)</th>
<th>Condition Factor (K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>February</td>
<td>87</td>
<td>89 (34–121)</td>
<td>9.4 (2.9–24.9)</td>
<td>0.96 (0.06–2.4)</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>80 (62–115)</td>
<td>5.7 (2.6–19.0)</td>
<td>1.04 (0.52–2.17)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>142</td>
<td>1.3 (1–5)</td>
<td>3.22 (0.49–9.0)</td>
</tr>
<tr>
<td>August</td>
<td>54</td>
<td>92 (62–190)</td>
<td>4.9 (5.2–20.3)</td>
<td>1.00 (0.37–1.54)</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>81 (62–106)</td>
<td>7.1 (8.0–16.0)</td>
<td>1.1 (0.78–1.5)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>96</td>
<td>3.2 (2–5)</td>
<td>3.22 (0.49–9.0)</td>
</tr>
<tr>
<td>December</td>
<td>28</td>
<td>88 (12–138)</td>
<td>4.9 (22–77)</td>
<td>1.5 (0.18–2.36)</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>81 (62–106)</td>
<td>7.1 (8.0–16.0)</td>
<td>1.1 (0.78–1.5)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>70</td>
<td>3.2 (2–5)</td>
<td>1.5 (0.18–2.36)</td>
</tr>
<tr>
<td>November</td>
<td>19</td>
<td>89 (34–121)</td>
<td>9.4 (2.9–24.9)</td>
<td>0.96 (0.06–2.4)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>90 (62–115)</td>
<td>5.7 (2.6–19.0)</td>
<td>1.04 (0.52–2.17)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>39</td>
<td>3.2 (2–5)</td>
<td>3.22 (0.49–9.0)</td>
</tr>
</tbody>
</table>

I, infected fish; NI, non-infected fish; F, female; M, male.
(90.4 ± 1.5 mm). However, because of the low sample size in certain age classes of infected fish, body lengths were considered according to age class, and differences were less apparent. Although the lengths of 2 + year-old infected roach (68.5 ± 1.5 mm) were significantly different (T = 2.43, P < 0.05) from their age-related non-infected counterparts (82.3 ± 5.5 mm), in older age classes, e.g. 3 year-old fish, no significant effect on the length of parasitised individuals (T = 0.21, P < 0.05) was noted.

Further analysis of the 2000–2001 cohort of fish also revealed a similar trend in the association with parasitisation and growth parameters. Young infected roach, 2 and 3 years old, rarely attained the same body weight as their non-infected counterparts (mean body mass: 2 + year-old infected 3.32 ± 0.24 g, non-infected 6.22 ± 1.6 g, T = 5.37, P > 0.05; 3 + year-old infected 6.18 ± 0.44 g, non-infected 7.71 ± 0.35 g, T = 2.73, P < 0.05). As with length, in 4 year-old fish there was no statistically significant difference between the body mass of infected and non-infected individuals (infected 8.39 ± 2.8 g, non-infected 10.79 ± 0.55 g, T = 0.85, P > 0.05).

The condition factor assumes that heavier fish of a given length are in better condition and eliminates variation attributable to gonadal development over the reproductive season. Because of the very small amount of gonadal tissue present in infected fish, and thus the problem of finding and confirming the presence of gonads without histological examination, the condition factor was calculated including the gonadal tissue in parasitised individuals. The sampled groups differed significantly in this parameter (T = 3.54, P < 0.05), i.e. non-infected fish K = 1.16 ± 0.15, infected fish K = 1.04 ± 0.03. Figure 2 shows the condition factor of fish according to age, showing lower K values in infected fish, reflecting the fact that non-infected individuals are in better condition, irrespective of age, than their infected counterparts.

**Gonadal development**

Because of the small amount of gonadal tissue in infected roach (weighing less than 0.1 g) GSI could not be correlated between infected and non-infected individuals. The maximum GSI obtained for non-infected individuals was 2% for immature fish to 15% in mature individuals. Natural variations were found within the sampled population, i.e. GSI leading up to spawning (February) varied between 0.1 and 14%, whereas post-spawning (August) GSI was not greater than 4%. The majority of non-infected fish achieved sexual maturation by 2 years of age (as determined by the presence of yolky oocytes) and all non-infected females were mature by 3 years of age.

In non-infected females, the ovaries contained large, mature eggs and several smaller, primary oocytes with only immature stages of development occurring post spawning. In contrast, in infected fish, only these immature stages of oogenesis were present throughout and no cyclical variations were recorded (see Arme 1968). Further quantification was performed in sections of the ovaries to determine the extent of oocyte development. No significant difference was found between the diameter of primary oocytes of infected females over all time-periods recorded (P > 0.05), revealing no cyclical changes. In contrast, the developing oocytes in uninfected fish showed a seasonal variation with a significant increase (P < 0.05) in yolk egg volume ratio towards the spawning season (December 12.88 ± 1.2 and February 21.23 ± 3.01).

**Pituitary LHβ content**

The use of a heterologous assay for carp LH was fully justified in view of the high level of sequence identity of the roach molecule (see below). A significant decrease in LH content (P < 0.05) was recorded in the pituitary glands of infected compared with non-infected roach. The average LH content of infected fish was almost 50% less than in non-infected individuals. Although individual variation was high, LH content of non-infected individuals was at its peak post-spawning (August) and lowest over the win-
ter period (December; Fig. 3). In contrast, infected fish consistently had lower LH levels at all seasonal time-points measured ($P < 0.05$) compared with non-infected individuals. Sexually mature (non-infected) fish showed little difference in LH content between the age groups ($P > 0.05$), although natural variations among individual fish were again evident.

**LH mRNA levels**

In conjunction with measuring LH content in pituitary glands, pituitary LH mRNA levels in infected and uninfected roach were determined using real-time PCR. In order to do this, fragments of the *R. rutilus* LHβ coding sequence and 18S rRNA were amplified from total RNA using degenerate primers and touchdown PCR. The fragments (337 and 1039 nucleotides respectively) obtained were cloned and sequenced (Genbank accession numbers: RrLH, AY770579; Rr18SrRNA, AY770580) and respectively showed 92% (102 of 111 amino acids) and 97% (1016 of 1039 nucleotides) identity to the orthologous sequences from *Cyprinus carpio*. When LHβ mRNA levels, normalized relative to the 18S rRNA levels and converted into relative copy number, were compared between infected and uninfected fish, the former contained approximately half the quantity of mRNA encoding this hormone ($P < 0.05$; Fig. 4).

**Discussion**

Our results have confirmed previous observations made by Arne (1968, 1997) on the biometric effects of *Ligula intestinalis* on its roach intermediate host. Importantly, it also revealed that the roach–parasite interaction under investigation is typical of that found in other sampled populations. In addition, GSI recorded in this infection suggested that non-infected host populations were undergoing normal reproductive cycles.

*Ligula intestinalis* could affect reproductive development of the fish at any level of the reproductive axis, from the first key hormones, gonadotrophin-releasing hormones (GnRH), to the gonads. For example, the expression of gonadotrophin hormones and their receptors (e.g. steroid receptors), which are necessary for the process of gametogenesis, may be disrupted, thus preventing brain activation and subsequent initiation of puberty. Furthermore, peripheral stimulators and inhibitors, active at all levels of the brain–pituitary–gonadal (BPG) axis, may be targets of the putative hormonal disruption by *Ligula*, which results in an inability of the gonads to respond to hormonal signals.

As has been noted previously by Kennedy *et al.* (2001) and Loot *et al.* (2001, 2002), our data suggest that *Ligula* may have a small inhibitory effect on body length, weight and condition in young fish (i.e. 2 years old). The fact that this inhibition was not observed when we compared older fish may arise from the negative effect of sexual maturation on growth and condition (e.g. Whalen & Parrish 1999). Indeed, sexual maturation will occur every year in non-infected fish but not in infected ones. This may explain why the growth curves of infected and non-infected fish become more similar in older fish. As in other vertebrates, body growth and condition have been suggested to act as triggers for the initiation of puberty in fish, although the mechanisms by which such a trigger is initiated is still largely unknown (for reviews see Peter *et al.* 1986, Huang *et al.* 1998). In the roach, our data also showed that *Ligula* infection exerts some inhibitory effects on body growth and condition, but these effects are small and would, therefore, not account for the complete blockade of puberty noted in ligulosed fish.

The reproductive system in fish is particularly susceptible to stress and immediate cessation of reproductive function is not uncommon when fish are brought into captivity (Wendelaar Bonga 1997). It may not be surprising, therefore, that the presence of a large parasite burden,

![Figure 3](https://www.reproduction-online.org/)

**Figure 3** Seasonal variations in roach pituitary gland hormonal LH content of both sexes as measured by RIA. Lowest LH levels were recorded in December, and were significantly lower in infected (open bars) compared with non-infected (solid bars) fish (August $P = 0.002$, December $P = 0.038$, February $P = 0.007$). The sample size is shown above each bar. Values are means ± S.E.M.

![Figure 4](https://www.reproduction-online.org/)

**Figure 4** mRNA levels of LH recorded in a pool of four pituitary glands by real-time RT-PCR. These data are presented as copy number of pituitary gland LH mRNA relative to non-infected glands. mRNA levels of infected fish were significantly lower than those of non-infected fish and parallel hormonal measurements.
which could be considered as a potent stressor, resulted in the observed dramatic effects on host reproduction. However, the relationship between Ligula and the induction of a possible stress effect on its fish host has been recently questioned by the work of Loot et al. (2001), in which the parasite induced no changes in the interrenal gland.

Previous observations have revealed that two GnRH forms (salmon and chicken) occurred in the brain of non-infected and infected roach (Williams et al. 1998). The distribution, cell number and staining intensity of both these types of neurones, which are considered to be the first steps in BPG axis activation, were not affected by Ligula (Penlington et al. 1997). However, seasonal variations in GnRH cell activity in non-infected fish were not investigated, and it cannot therefore be deduced that GnRH cells (or GnRH release) are not affected in infected fish.

Our results have shown that the pituitary gland of infected fish is still capable of synthesising LH as determined by real-time PCR and RIA. Whilst it is true that gonadotrophs are much reduced in number, the cells that are present do appear to be functional, indicating that Ligula infection neither completely prevents gonadotroph differentiation nor basal activity. However, seasonal variations in pituitary LH content observed in non-infected fish were absent in infected roach. A significant 50% mean reduction in pituitary LH content was found in infected fish as compared with non-infected individuals. In addition, real-time RT-PCR supported these observations and also showed a 50% reduction in pituitary LHβ mRNA levels in infected males and females. This suggested that Ligula infection decreases LH synthesis by inhibiting its expression and indicates that the levels of gonadotropin-producing cells being affected by parasitisation are critical to normal reproductive function.

Further studies are required to ascertain the mechanisms by which Ligula induces its inhibitory effect on roach LH production. It has also been noted that in other teleost species, such as the goldfish, sex pheromones (predominantly 17,20β-progesterone and prostaglandin F2α) are a stimulus for inducing LH secretion and milt volume in males (Stacey et al. 1994, Zheng & Stacey 1997). Given that fish infected with Ligula intestinalis do not exhibit normal behaviour patterns in terms of shoaling (e.g. Orr 1966), pheromonal stimuli which would normally be received within the group-shoaling situation are absent from infected individuals, which may enhance the delay in puberty (Francis et al. 1993). This abnormal behaviour may also expose roach to different light intensities, a parameter vital in the control of the reproductive cycle in fish (Bromage et al. 1991, Davies et al. 1999, Kah et al. 1999).

Ligula infection could also affect LH production by acting directly on the gonadotrophs. Indeed, preliminary in vitro studies from our group (data not shown), using primary culture of pituitary cells from another teleost (European eel, Anguilla anguilla) suggested that Ligula excretory/secretory (E/S) products may affect LH production directly at the pituitary cell level. However, an apparently increased LH production in the eel suggested possible species differences in the action on gonadotroph activity. Although this effect was dose dependent, significant differences were found between Ligula and a related tapeworm species, Schistoccephalus solidus. This not only supports the hypothesis by Arme (1997) that reproductive inhibitory effects are specific to Ligula, but also suggests that effects of the parasite extend to non-host species (e.g. the European eel), implying a general endocrine effect. Further studies are required to establish if the effect of E/S products on roach LH production is directed at the pituitary cell level, or mediated via dual neuroendocrine control. The latter has been demonstrated in other cyprinids where positive and negative responses have been noted for GnRH and dopamine respectively (for review see Peter et al. 1986).

Investigations of the effect of Ligula on the production of the other gonadotrophin (follicle-stimulating hormone) are also required, especially considering the potential effect of the parasites on the early stages of gametogenesis.

We have also demonstrated that infected roach have a decreased condition factor, weight, length and gonadal development with respect to their age- and season-matched uninfected counterparts. In addition, we have for the first time revealed that the LH pituitary content and mRNA levels are also significantly decreased in infected individuals. Although the mode of action of the parasite remains elusive, it is clear that the pituitary gland morphology and gonadotrophic hormone production are affected by the parasite. Whether this is mediated by direct effects of Ligula products or general endocrine disruption requires elucidation. However, it is interesting to speculate that the isolation and characterisation of active parasite E/S substances (if they exist) may lead to the identification of novel contraceptive compounds.

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References


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