

Stressed? Looking for Solutions? Harmonease™ Chewable Tablets

for the management of stress related behaviors in dogs



References

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- ⁴ *Expectations of biologically active compounds of the genus Magnolia in biomedicine*. Patočka, Jiří; Jakl, Jiří; Strunecká, Anna. Journal of Applied Biomedicine 4:171-178, 2006.
- ⁵ *Overview of the Pharmacological Features of Honokiol*. Maruyama, Yuri; Kuribara, Hisashi. CNS Drug Reviews, Vol 6, No 1, pps 35-44. 2000.
- ⁶ *Relora® Professional Detail* by Next Pharmaceuticals, Inc. July 6, 2006.
- ⁷ *Antidepressant-like effects of the mixture of honokiol and magnolol from the barks of **Magnolia officinalis** in stressed rodents*. Xu, Qun; Yi, Li-Tao; Ying, Pan; Wang, Xing; Li, Yu-Cheng; Li, Jian-Mei; Wang, Cai-Ping; Kong, Ling-Dong. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 32 (2008) 715-720.

See Harmoneasevet.com or vpl.com websites for more information and special offers.

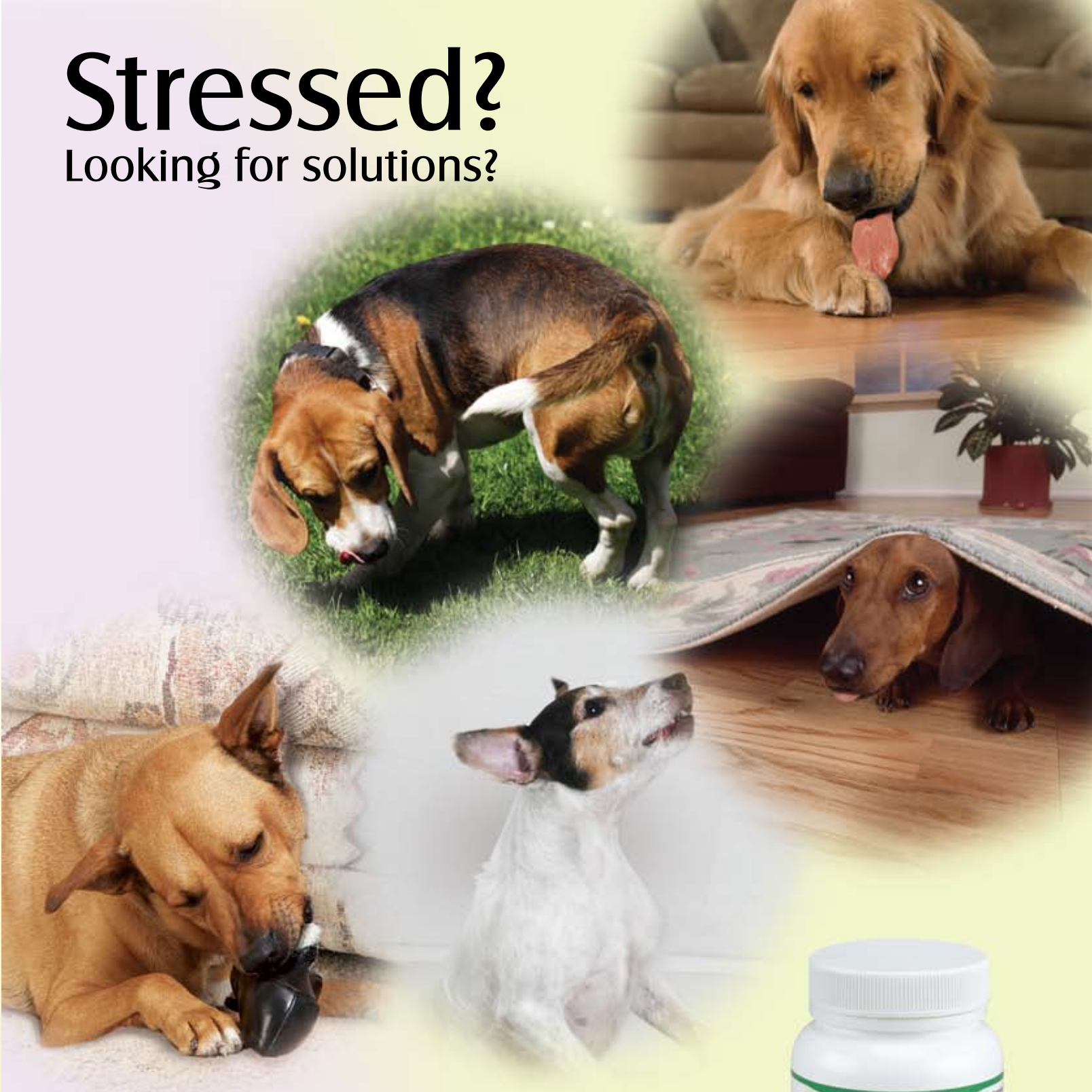


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Stressed?

Looking for solutions?



Introducing



Harmonease™

Chewable Tablets 500 mg

for the management of stress related behaviors in dogs



Harmonease™ Chewable Tablets

What are some stress related behaviors?¹

- Excessive chewing or licking at self, other animals or objects
- Compulsive movements, such as circling, digging, and covering

What are some neurotransmitters involved in stress?²

GABA – gamma amino butyric acid

- Most widespread neurotransmitter in the brain, synthesized from glutamic acid
- Causes mostly inhibitory effects

Glutamate

- Excitatory amino acid neurotransmitter
- May be produced in abnormal levels in stress related disorders

Serotonin (5-hydroxytryptamine or 5-HT)

- Synthesized from tryptophan
- Plays a major role in the sleep/wake cycle, mood and emotion
- Increase of serotonin may be associated with activation of hypothalamic-pituitary-adrenal (HPA) axis
- Decrease in serotonin may lead to lethargy, increased stress and aggression



What is Harmonease™?

Harmonease™ is a natural proprietary blend of a patented extract of *Magnolia officinalis* and a proprietary extract of *Phellodendron amurense*.

Phellodendron amurense has demonstrated significant anti-stress effects in rodent tests.³

Magnolia officinalis contains a mixture of *honokiol* and *magnolol*, both of which have been identified in vitro as modulators of the GABA_A receptors for activity to decrease stress.⁴ *Honokiol* has a comparatively lower risk of causing lethargy and muscle relaxation.⁵

The unique combination of these two fractions in Harmonease™ takes advantage of a synergistic association. Concurrent binding affinities at five selective targets suggest a high level of response in a number of stress related behaviors.⁶

Significant complementary binding profile between Harmonease ingredients and targets associated with stress.

Targets	<i>Magnolia</i> fraction	<i>Phellodendron</i> fraction
Adenosine A ₁	X	X
Adrenergic α 2		X
GABA _A agonist	X	X
Glutamate NMDA	X	
Serotonin transporter	X	X

Harmonease™ Chewable Tablets

Active ingredients

Extracts of *Magnolia officinalis* and *Phellodendron amurense*.....500 mg

Honokiol standardized to 9.5 mg

- Composed of natural ingredients
- Formulated as convenient once-a-day chewable tablets
- Should be used with appropriate behavior modification

Dose

For dogs up to 50 lbs, give ½ tablet once a day

For dogs over 50 lbs, give 1 tablet once a day

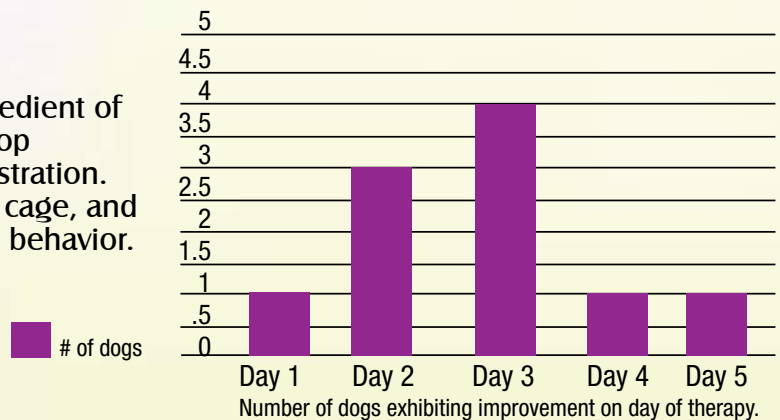


Rodent Studies

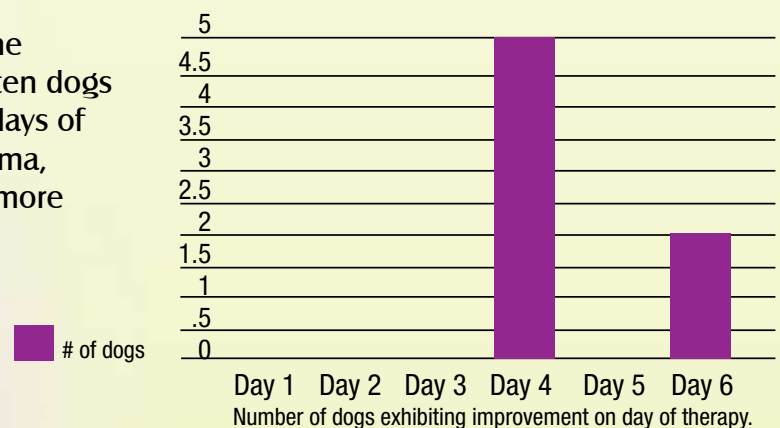
A mixture of *honokiol* and *magnolol* significantly attenuated chronic mild stress induced decreases of serotonin (5-hydroxytryptamine or 5-HT) in the brain of rats. It also reduced elevated corticosterone concentrations in serum to normalize the hypothalamic-pituitary-adrenal (HPA) hyperactivity in the chronically mild stressed rats.⁷

Efficacy Studies*

In a trial with 10 kenneled dogs, the active ingredient of Harmonease™ in powder form was shown to stop stereotypical behaviors within 5 days of administration. Behaviors included lick granuloma, spinning in cage, and cowering. Some dogs exhibited more than one behavior.



In another trial with 10 kenneled dogs, using the chewable form of Harmonease™, seven out of ten dogs stopped their stereotypical behaviors within 6 days of administration. Behaviors included lick granuloma, spinning, and cowering. Some dogs exhibited more than one behavior.



Safety Study*

Thirty-two (32) dogs (8 dogs per group) were selected for treatment and randomly assigned 0x, 1x, 3x or 5x the label dose of Harmonease™ for 28 days. Some dogs experienced mild and self limiting vomiting and diarrhea, mostly in the 5x group.

Palatability Study*

In an acceptance test with 20 dogs in a 2 day trial, all dogs ate the tablets offered to them.