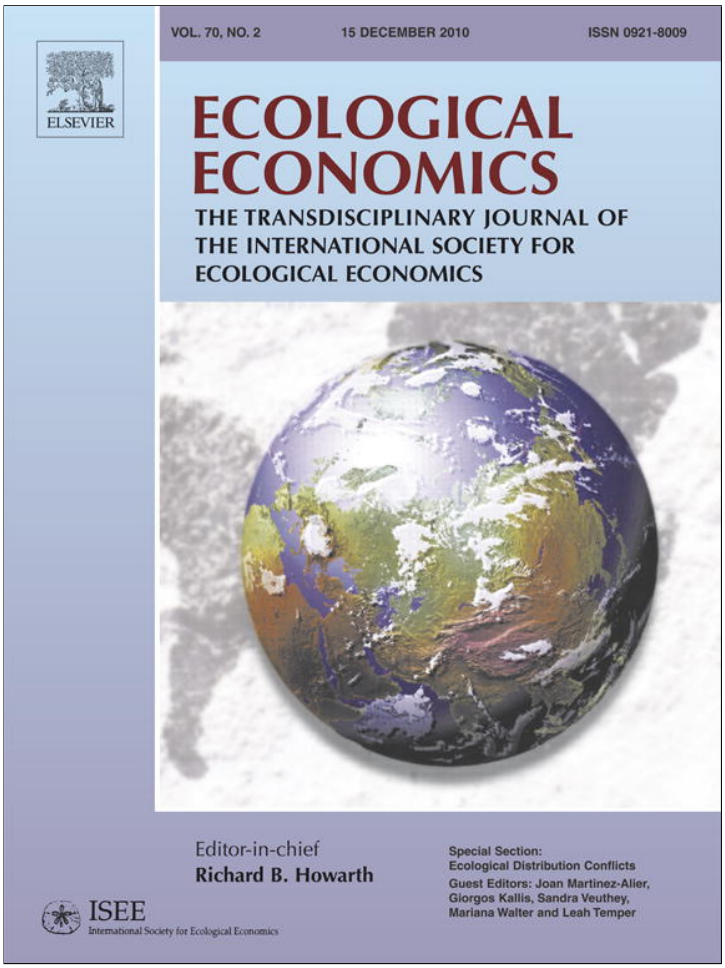

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Analysis

The pharmaceutical value of marine biodiversity for anti-cancer drug discovery

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ABSTRACT

Marine biodiversity is a resource of enormous importance to human societies that provides critical ecosystem services. Economic valuation of some services has been utilized to promote conservation initiatives by revealing a tangible and causative link between biodiversity declines and economic losses. Other ecosystem services have eluded valuation, including the value of the sea as a repository of novel pharmaceuticals. Here, we provide the first global estimate of the number, source and market value of undiscovered oncology drugs based on empirical data, industry statistics and conservative modelling assumptions. We report US $563 billion–5.69 trillion attributable to anti-cancer drugs of marine origin pending discovery, revealing a new and substantial at-risk ecosystem service value. Our model predicted 253,120–594,232 novel chemicals in marine organisms; 90.4–92.6% of these compounds remain undiscovered. A total of 55 to 214 new anti-cancer drugs were predicted to reach the market sourced primarily from animal phyla (Chordata, Mollusca, Porifera, and Byrozoa) and microbial phyla (Proteobacteria and Cyanobacteria). While no single aspect of extractive marine resource value should be relied upon to account for the opportunity costs of conservation initiatives, the application of valuation models to ecosystem services further reveals the true, irreversible economic cost of habitat degradation and biodiversity declines.

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1. Introduction

The ultimate value of the world's natural resources is infinite, given that ecosystem services such as climate regulation, food supply and water purification are prerequisites for the persistence of human societies. However, efforts to conserve ecosystems and protect their services confer immediate implementation and opportunity costs on society (James et al., 1999) that often take precedence in resource usage and management decisions (Balmford et al., 2002). Indeed, the immediate and apparent benefits of use commonly gain favor over the long-term and more obscure costs of using a given resource, which can lead to the over-use and exploitation of resources from the marine environment. The resulting loss of marine biodiversity, triggered on a global scale by direct and indirect anthropogenic disturbances, has led to exponential reductions in service yield, resource devaluation and, if unabated, resource collapse (Worm et al., 2006). Specific enumeration of ecosystem services and their economic value is thus crucial to help resource managers, policymakers and stakeholders make informed decisions regarding the economic consequences of management alternatives. Moreover, uncovering previously unknown components of *in situ* natural resource value can be used to raise public awareness of the real economic costs associated with resource usage beyond the regenerative capacity of ecosystems.

Economic valuations of marine resources have commonly focused on fisheries, tourism, and shoreline protection in coastal ecosystems (Brander et al., 2007; Holmlund and Hammer, 1999) and on climate regulation, nutrient cycling and waste bioremediation in open oceans (de Groot et al., 2002). In addition to these well-studied ecosystem services, marine organisms are a rich source of novel chemical compounds, called marine natural products (MNPs), that are produced mainly as defense mechanisms toward predators, competitors and fouling organisms (Pawlik, 1993; Hay, 1996; Paul and Ritson-Williams, 2008). The application of these compounds to biomedical research and drug development has revealed that the structural complexity, novelty and diversity of MNPs can translate into new pharmaceuticals for the treatment of human diseases, mostly as chemotherapeutic agents (Blunt et al., 2009; Maggon, 2005). In fact, 2 MNPs have reached the market as anti-cancer treatments and approximately 3 of every 4 new anti-cancer drugs introduced over the past 6 decades have been developed from natural products (marine and terrestrial), commonly as derivatives or synthetic mimics (Newman and Cragg, 2007).

Despite the importance of natural products for pharmaceutical research and economic benefits to human society, the global value of marine biodiversity as a source of novel MNPs has never been estimated. To our knowledge, only one study has performed a MNP valuation on a local scale, focusing on coral reef biodiversity in

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Montego Bay, Jamaica and reporting a base case value of US $70 million (Ruitenbeek and Carter, 1999). In contrast, several studies have predicted the total value of medicines from tropical forests, with estimates ranging from US$2.8 billion (use value; Mendelsohn and Balick, 1995) to US$420 billion (use and social values; Pearce and Puroshothaman, 1992). Simpson et al (1996) derived the value of marginal species, and by extension a hectare of land for bioprospecting, using a simple model of demand for pharmaceutical research. Based on the marginal contribution of single species to the probability that a valuable product will be discovered, these authors demonstrate that the value of a marginal species to private sector research is expected to be negligible. Craft and Simpson (2001) illustrated similar findings by applying models of competition among products. In addition, Kassar and Lasserre (2004) provided a theoretical real options model for deriving the expected present value of a set of species (value less costs of preservation) by optimally choosing the stochastic dates at which each species is allowed to go extinct. While useful for its intuitive results and financial investment analogues, such an approach is intractable for empirical considerations of value. Indeed, operationalizing such a model, even for a single ecosystem, requires a level of understanding of value and cost relationships that does not currently exist.

Providing an empirical understanding of the economic value of biodiversity in general and MNPs in particular is confounded by the complexity of ecosystem structure and function and the uncertainly regarding current and future needs for these genetic resources. However, attempts to value marine biodiversity and marine resource services should not be abandoned and become increasingly important in the face of global ecosystem declines (Bockstael et al., 2000). Further, these values represent irreversible costs of habitat destruction and biodiversity loss, a category of costs that bears special consideration in decision-making processes (Arrow and Fisher, 1974). Similarly, biodiversity preservation represents a source of irreversible benefits, a category that outweighs reversible ones in cost–benefit analyses (Wesseler, 2009).

This study extends the current body of knowledge regarding the overall value of marine services by examining the market value of species preservation for pharmaceutical use. Specifically, the market value of marine biodiversity as a source of novel oncology drugs was calculated considering the phylum-specific potential to produce MNPs, market hit rates for MNPs, and the lifetime net present value (NPV) of new anti-cancer drugs. A real option approach for the global supply of marine species was not conducted and surmounting the difficulties inherent in parameterizing such a model is beyond the scope of our study, though an important research avenue for future work. Rather, the values derived herein may be described as expected future commercial (use) values or at-risk market values, but might also be classified as biodiversity option values (Weisbrod, 1964). Our empirical approach is similar to that of Pearce and Puroshothaman (1992), thus the value estimates we derive correspond more closely to the former category. More generally, the resulting pharmaceutical values fit into the domain of option valuation, since the loss of this value is irreversible, and since we consider a pool of species, their possible uses and an assessment of the probability of future discoveries (Kassar and Lasserre, 2004).

2. Materials and Methods

2.1. Phylum Potential to Produce MNPs

The potential of each phylum to produce new MNPs was determined by dividing the number of compounds isolated for each phylum by the percentage of species of that same phylum investigated to date *(#MNP/%Species)*. The database MarinLit (ver. vpc13.5) was examined to determine the total number of species per phylum that have been chemically studied and the number of natural products *(#MNP)* that have been isolated as a result of those studies. The percentage of species studied *(%Species)* was determined by dividing the number of analyzed species in MarinLit by the total number of described marine species for each phylum. Estimates of eukaryotic biodiversity were taken from the World Registry of Marine Species (WoRMS) database (SMEBD, 2009), considering two values for each phylum: 1) 'valid species' — records validated by a recognized taxonomic expert, and 2) 'all species' — records officially described yet awaiting expert validation. Phylum Magnoliophyta was an exception, since no records existed in WoRMS, and biodiversity estimates were obtained from AlgaeBase (Guiry and Guiry, 2009). Estimates of prokaryotic biodiversity were taken from the Catalogue of Life database (Brisby et al., 2009) and GenBank (NCBI) database (Benson et al., 2008). The former provided lower bound estimates of bacterial biodiversity based on cultured strains; the latter provided upper bound estimates of bacterial biodiversity based on molecular data. To assess marine microbial genetic diversity, a nucleotide search was conducted in GenBank using the parameters "16S AND 'X' AND (marine OR coastal OR ocean OR sediment)" where 'X' was replaced with each bacteria phylum.

2.2. MNPs in Clinical Trials and Market Hit Rate Calculations

To determine the number of marine natural products and their synthetic compounds in clinical and pre-clinical trials, published literature was extensively reviewed for past and present compounds with anti-cancer properties and the classification of their source organisms (Table S1). MNP data were grouped taxonomically (by phyla), as accepted by the WoRMS database. In the rare cases where a compound was isolated from organisms belonging to two different phyla (e.g. Zalypsis, Table S1), each phylum scored half a point to avoid overestimating the importance of the phyla and the drug. Phylum-specific clinical trial hit rates were calculated as the number of MNPs in clinical trials divided by total MNPs described for each phylum. Obtaining empirical market hit rates for most phyla was not possible, since only 2 MNPs have reached the market to date. In these two cases, the empirical clinical trial to market drug ratio was 5.25:1, similar to the 5:1 industry-wide estimate for clinical trial to market drug ratio (PhRMA, 2008). Therefore, phylum-specific market hit rates (*MktHR*) were estimated by dividing empirical clinical trial hit rates by 5.

2.3. Net Present Value of New Oncology Drugs

The net present value (*NPV*) of cash flows from investment in a new oncology drug was calculated as:

$$NPV = \sum_{t=0}^{n} \frac{Cf_t}{(1+i)^t}$$

where n is the patent life, Cf_t is the cash flow at time t, and i is the applied discount rate. Average patent life for a new pharmaceutical (11 years) was taken from the Pharmaceutical Research and Manufacturers of America's 2008 Industry Profile (PhRMA, 2008). Expected cash flows were forecasted from historical oncology drug revenue data. Average annual revenues[2] were calculated for 49 anti-cancer drugs (representing 13 pharmaceutical companies) from 1999 to 2008, as reported in SEC filings (10 K) and corporate annual reports (Table S2). Data were converted to US dollars, where necessary, using

[2] Median annual revenue calculations reduced output values of the model by ~30% (Lifetime NPV = US$7.1–18.0 billion; Pharmaceutical value = US$391 billion–4.04 trillion) compared to average annual revenue calculations, due to a limited number of high-revenue (blockbuster) drugs inflating average values. We argue that average values represent a more accurate prediction of future MNP revenues, with their unique compounds, complex structures and novel mechanisms of action more likely to yield high-revenue medicines.

historical exchange rates for each respective year (Federal Reserve Statistical Release H.10, 2009). These data were then used to calculate the average growth in oncology drug revenues over the past decade and to forecast the drug sales over the next 11 years. Our forecast model assumed that future market demand for anti-cancer drugs will follow the same trend as the prior 10-year period, and is subject to changes in the incidence of disease, breakthrough discoveries and cures obtained from other sources. Should a cure for cancer be derived from MNPs, the value estimates derived here can be considered severe underestimates of value, while a cure from non-MNP sources would diminish or eliminate MNP value. Detailed analysis of such probabilities and their effect on market conditions is beyond the scope of this study.

Development expenses (US$1.318 billion), including discovery costs and costs of failure, were taken from the Pharmaceutical Research and Manufacturers of America's 2008 Industry Profile (PhRMA, 2008) and DiMasi and Grabowski (2007) and were considered as one-time, upfront investment costs in NPV calculations. The future time path of these costs is subject to the effects of changes in marginal returns to discovery and development inputs that facilitate the transition of natural compounds to marketable products, as well as to changes in returns to firm and industry scale. While we can hypothesize that the latter of these returns likely portends lower costs over time as firms and the industry expand, we cannot hypothesize *a priori* the future path of marginal returns to variable inputs because MNP markets and extraction technologies are still emerging. As such, our assumption of constant costs over the relevant time frame can be considered a conservative approximation.

A sensitivity analysis was conducted using discount rates from 2% to 15%, spanning the range of typical discount rates in developed and developing countries (Zhuang et al., 2007). Discount rates on the lower end of this range reflect low-risk private investment decisions by pharmaceutical companies in developed nations, while higher rates approximate high-risk private ventures or social discount rates for conservation decisions in developing nations.

2.4. Pharmaceutical Value Calculations

The current pharmaceutical value (*PhV*) of marine organisms to produce new oncology drugs was calculated as:

$$PhV = \frac{\#MNP}{\%Species} \times MktHR \times NPV$$

where, *#MNP* is the number of MNPs described to date, *%Species* is the percentage of marine species investigated for MNPs, *MktHR* is the probability of a new MNP reaching the market (i.e., market hit-rate), and *NPV* is the net present value of a new anti-cancer drug in the market. Phylum-specific *PhV*s were calculated individually and summed to yield the potential market value of marine biodiversity for anti-cancer drug discovery.

3. Results

3.1. Phylum Potential to Produce MNPs

The described chemical diversity of the sea totalled 18,552 MNPs from 27 marine phyla, dominated by sponge (n = 6605; 35.6% total) and cnidarian-derived (n = 3454; 18.6% total) compounds (Fig. 1). In the major of marine phyla (n = 14; 51.9%), less than 30 species have been investigated for MNPs. Of the top 10 most studied phyla (>200 species examined), half (n = 5) were from the kingdom Animalia, along with a single representative from the kingdoms Plantae, Protoctista, Fungi, Monera and Chromista. Independent of sample size, a consistent marginal contribution of 2.12 new MNPs per species examined was revealed across all taxa (Fig. 1; Linear Regression, $P<0.001$, $R^2 = 0.99$), from less sampled phyla (e.g., Magnoliophyta, 8 MNPs from 4 species) to well-sampled phyla (e.g., Porifera 6605 MNPs from 3130 species).

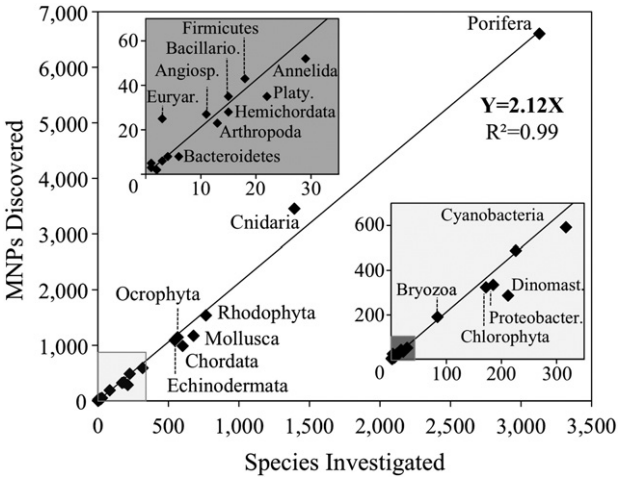

Fig. 1. Linear regression of described MNP diversity and number of investigated marine species for 27 marine phyla. Main panel depicts the consistent linear relationship between the number of MNPs discovered and the number of species studied. Insets magnify lower axis scales (axis units same as main panel). Angiospermophyta (Angiosperm.), Bacillariophyta (Bacillario.), Dinomastigota (Dinomast.), Euryarchaeota (Euryarch.), Platyhelminthes (Platy.), and Proteobacteria (Proteobacter.).

3.2. Current and Predicted MNP Drug Discovery Pipeline

Analysis of the drug discovery pipeline revealed 118 MNPs in pre-clinical trials, 22 MNPs in clinical trials and 2 MNPs in the market (Fig. 2). MNPs in pre-clinical trials were derived from 16 phyla, led by Porifera (n = 46, 39.0% total), Chordata (n = 11.5, 9.7%) and Ascomycota (n = 11, 9.3%). MNPs in clinical trials were derived from 8 phyla, led by Porifera (n = 7.5, 34.1% total), Mollusca (n = 4, 18.2%), Chordata (n = 3, 13.6%) and Proteobacteria (n = 3, 13.6%). MNPs in the market were derived from 2 phyla, with 1 compound (Cytarabine®) from Porifera and 1 compound (Yondelis™) from Chordata (Table S1).

Pre-clinical hit rates average 1.18 ± 1.00% (±1SD) across all marine phyla, ranging from 0.20% in Cnidaria to 3.57% in Hemichordata (Table S3). Clinical hit rates averaged 0.36 ± 0.25%, ranging from 0.11% in Porifera to 0.90% in Proteobacteria (Table S3). Empirical market hit rates were only available for Porifera (0.02%) and Chordata (0.10%) and estimated market hit rates averaged 0.07 ± 0.05%, ranging from 0.02% in Porifera to 0.18% in Proteobacteria (Table S3).

Predicted total MNPs and future oncology medicine yields revealed that 7.3–9.4% of total marine biodiversity has been investigated for chemical diversity, resulting in 253,120–594,232 MNPs pending discovery (Table 1). Of these compounds, derived hit rates predict that 55–214 will pass clinical trials and reach the market as oncology drugs.

3.3. Oncology Drug Revenues and Lifetime NPV

Future cash flows were forecasted from oncology drug revenues over the past decade, averaging a 13% year-on-year growth from 1999 to 2008 and reaching US$1.32 billion by 2008 (Fig. 3). Individual drug sales varied within each year, often depending on the drug's position in the product life cycle, with maximum revenues from blockbuster drugs increasing 370% over the 10-year period and reaching US $5.48 billion by 2008 (Fig. 3). The lifetime NPV of a new oncology drug was US$10.3–26.6 billion, calculated using discount rates from 2–15%, an upfront development cost of US$1.318 billion and a patent life of 11 years.

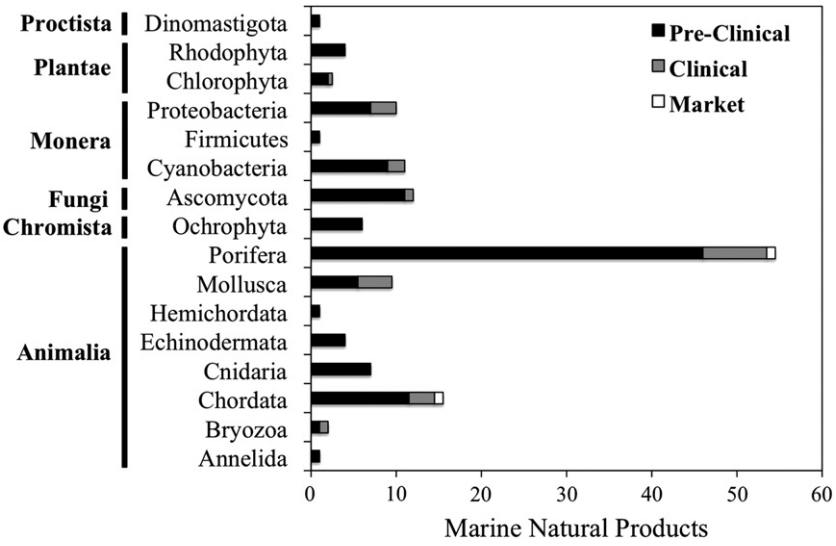

Fig. 2. Current status of MNPs in the drug discovery pipeline. Number of MNPs residing in pre-clinical trials (dark grey), clinical studies (light grey) and the market (white) are shown categorized taxonomically by kingdom and phylum.

3.4. Pharmaceutical Value of the Sea

The pharmaceutical value of marine biodiversity for anti-cancer drug discovery ranged from US$563 billion–5.69 trillion, varying with total biodiversity estimates and discount rates applied to NPV calculations (Table S4, Fig. S1). Under lower biodiversity estimates, the kingdom Animalia contributed three-fourths of the pharmaceutical value, followed by kingdom Monera (Fig. 4A); whereas under upper biodiversity estimates this trend was reversed (Fig. 4B). Both estimates revealed a marginal contribution by kingdoms Plantae (<2%) and Fungi (<1%), and no contribution by the kingdoms Chromista and Protoctista. The relative contribution of each phylum

Table 1
Predicted number of total MNPs per marine phylum and kingdom, calculated using total MNPs described to date (No. MNP), total species investigated to date (No. species) and total extant species (Species) under lower and upper global biodiversity estimates. The numbers in italics denote average values.

Kingdom	Phylum	No. MNPs	No. species	Species		%Species		Total MNPs	
				Lower Est	*Upper Est*	*Lower Est*	*Upper Est*	*Lower Est*	*Upper Est*
Animalia	Annelida	52	29	12,555	18,970	0.23%	0.15%	22,512	34,015
Animalia	Arthropoda	23	13	33,683	40,246	0.04%	0.03%	59,593	71,204
Animalia	Bryozoa	191	84	1359	1494	6.18%	5.62%	3090	3397
Animalia	Chordata	990	601	21,375	49,854	2.81%	1.21%	35,210	82,122
Animalia	Cnidaria	3454	1393	10,806	12,383	12.89%	11.25%	26,794	30,704
Animalia	Echinodermata	1091	545	5637	10,588	9.67%	5.15%	11,284	21,195
Animalia	Hemichordata	28	15	107	118	14.02%	12.71%	200	220
Animalia	Mollusca	1173	678	10,967	12,995	6.18%	5.22%	18,974	22,483
Animalia	Nematoda	2	2	5541	5895	0.04%	0.03%	5541	5895
Animalia	Platyhelminthes	35	22	2966	3332	0.74%	0.66%	4719	5301
Animalia	Porifera	6605	3130	8085	15,502	38.71%	20.19%	17,061	32,713
Archaea	Euryarchaeota	25	3	281	17,110	1.07%	0.02%	2342	142,583
Chromista	Bacillariophyta	35	15	1833	2783	0.82%	0.54%	4277	6494
Chromista	Ochrophyta	1146	566	2162	2269	26.18%	24.94%	4377	4594
Fungi	Ascomycota	488	226	394	410	57.36%	55.12%	851	885
Fungi	Mitosporic Fungi	6	3	46	49	6.52%	6.12%	92	98
Monera	Bacteroidetes	8	6	416	6416	1.44%	0.09%	555	8555
Monera	Cyanobacteria	592	317	2921	8113	10.85%	3.91%	5455	15,151
Monera	Firmicutes	43	18	1672	5196	1.08%	0.35%	3994	12,413
Monera	Proteobacteria	335	185	2549	38,928	7.26%	0.48%	4616	70,491
Plantae	Angiospermophyta	27	11	156	206	7.05%	5.34%	383	506
Plantae	Chlorophyta	324	172	1776	1895	9.68%	9.08%	3345	3570
Plantae	Magnoliophyta	8	4	60	60	6.67%	6.67%	120	120
Plantae	Rhodophyta	1540	766	6279	6468	12.20%	11.84%	12,624	13,004
Protoctista	Ciliophora	5	1	500	594	0.20%	0.17%	2500	2970
Protoctista	Dinomastigota	287	212	1840	2513	11.52%	8.44%	2491	3402
Protoctista	Labyrinthulata	3	1	40	49	2.50%	2.04%	120	147
Protoctista	Unclassified	36	25	–	–	–	–	–	–
Animalia Total (*Average*) =		13,644	6512	113,081	171,377	*(8.32%)*	*(5.66%)*	204,978	309,250
Archaea Total (*Average*) =		25	3	281	17,110	*(1.07%)*	*(0.02%)*	2342	142,583
Chromista Total (*Average*) =		1181	581	3995	5052	*(13.50%)*	*(12.74%)*	8654	11,088
Fungi Total (*Average*) =		494	229	440	459	*(31.94%)*	*(30.62%)*	943	983
Monera Total (*Average*) =		978	526	7558	58,653	*(5.16%)*	*(1.21%)*	14,620	106,610
Plantae Total (*Average*) =		1899	953	8271	8629	*(8.90%)*	*(8.23%)*	16,472	17,199
Protoctista Total (*Average*) =		331	239	2380	3156	*(4.74%)*	*(3.55%)*	5111	6519
Grand Total (*Average*) =		18,552	9043	135,946	264,376	*(9.40%)*	*(7.31%)*	253,120	594,232

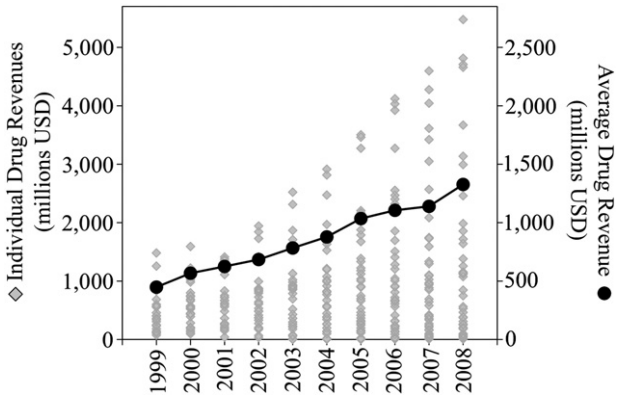

Fig. 3. Annual revenues and historical growth of oncology drugs over the past decade. The data are from 49 anti-cancer pharmaceuticals, representing 13 companies. The black circles depict annual averages and grey diamonds individual drug revenues.

varied within each kingdom, with phylum Chordata yielding most of the value attributed to kingdom Animalia, and phylum Proteobacteria to kingdom Monera (Fig. 4; Table S4).

4. Discussion

Any estimation of value on a global scale is contingent upon numerous assumptions. Our valuation model provided a baseline estimate of market value utilizing empirical data, industry statistics and conservative assumptions. Hit-rate calculations assumed that all described MNPs have been screened for anti-cancer activity, which is unlikely given the minimal yield of compounds from source organisms and the large amount required for pharmaceutical testing. In addition, only marine phyla with MNPs in clinical trials (n = 8) were included, although an additional 8 phyla have 25 compounds in pre-clinical trials. Calculations were also based on described biodiversity, rather than total (extant) biodiversity, due to the high variability of global estimates. For instance, bacterial biodiversity values considered in this study ($2.5–4.6 \times 10^3$ species) likely underestimate total marine bacterial biodiversity, which may contain up to 2×10^6 taxa (Curtis et al., 2002). Finally, pharmaceutical revenues from oncology drugs were considered only under patent exclusivity, while total economic activity from drug sales continues off patent through generic products. Additional screening of described MNPs, progression of pre-clinical MNPs through the drug pipeline and further description of global biodiversity are expected to increase the pharmaceutical value estimates reported herein.

Another critical assumption of our model was that the discovery and development trends observed for described MNPs were representative of all MNPs pending discovery. Specifically, global estimates were calculated by extrapolating the chemical diversity of marine organisms and the clinical success rates of described MNPs. Evidence to date corroborated the former assumption, with a consistent marginal contribution of 2.12 new MNPs per species examined across all marine taxa, independent of the number of species sampled (Fig. 1). Further, clinical success rates for MNPs are at present contingent more upon technology than bioactivity, since progression through the drug discovery pipeline requires large amounts of active compounds. Without the ability to produce MNPs by laboratory

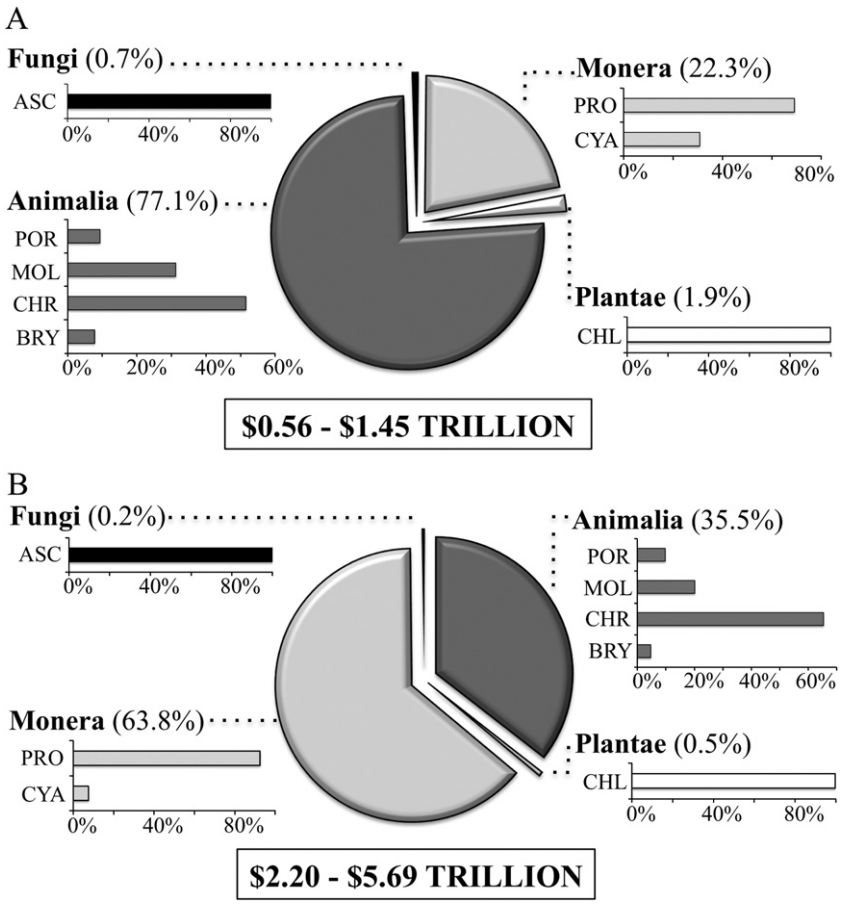

Fig. 4. Pharmaceutical value of new oncology drugs pending discovery from marine organisms. The pie charts depict the relative contribution of each kingdom to overall value under lower (A) and upper (B) biodiversity estimates. The bar graphs display the percentage contribution of individual phyla within each kingdom. Ascomycota (ASC), Bryozoa (BRY), Chlorophyta (CHL), Cyanobacteria (CYA), Chordata (CHR), Mollusca (MOL), Porifera (POR), and Proteobacteria (PRO).

synthesis, even the most promising compounds are orphaned or abandoned.

Indeed, one of the major limitations the natural product discovery industry has traditionally faced is acquiring sufficient yields of MNPs to undergo clinical trials (Cragg et al., 1993). However, technological advances in genetic techniques targeting the identification and heterologous expression of biosynthetic gene clusters are prompting a new wave pharmaceutical interest in the sea (Li and Vederas, 2009). Metagenomic searches have yielded the isolation of biosynthetic clusters from uncultured bacteria and revealed the true origin of many MNPs (Piel et al., 2004). Consequently, the successful heterologous expression of some biosynthetic genes in culturable bacteria has already generated the needed long-term supply for a few potential drugs (Schmidt et al., 2005). New compounds can also be generated through the genetic manipulation of original MNP biosynthetic pathways or by combining biosynthetic genes from different source organisms (Hwang et al., 1995; Julsing et al., 2006; Rodriguez and McDaniel, 2001; Salas et al., 2001). Although several technical limitations have yet to be overcome, further development of these techniques may considerably increase the pool of available MNPs for pharmaceutical research, the number of anti-cancer drugs from marine origin that reach the market, and the overall pharmaceutical value of the sea.

A final assumption of our valuation model concerns the existence and incidence of redundancy or substitutability among MNPs investigated for anti-cancer activity and their effect on the overall market value of species for pharmaceutical development. The direction of the effect of redundancy on the value of *in situ* biodiversity is currently ambiguous. Notions that redundancy reduces marginal value (Simpson et al., 1996; Craft and Simpson, 2001) are plausible from a consumer standpoint, but ignore the possibility of species interdependencies. If two species contain the same compound and are fully independent in an ecological context, then the elimination of one may result in no net loss of MNPs and no value loss to society (i.e., redundancy of product outputs). However, chemical or genetic redundancy does not imply species redundancy. If two species contribute to the functionality of an ecosystem, then the loss of one may induce the loss of the other, or, in the case of inverse complementarities, improve the viability of the other (Gitay et al., 1996). Moreover, under conditions of uncertainty, redundancy can create value by facilitating product development and for insurance reasons (Kassar and Lasserre, 2004). Thus, the effect of redundancy on the value of MNPs specifically, and species more generally, is context-dependent and most likely ecosystem-, species- and compound-specific. Given this uncertainty and the effectively global scope of our analysis, the present valuation model did not parameterize redundancy and focused on variables derived from empirical data. In practice, the incorrect estimation of such parameters produces large differences in valuation results (Costello and Ward, 2006) and may thus obscure valuation studies until redundancy quantification is better developed. In theory, the underlying concept of redundancy in conservation is questionable, since the empirical identification and measurement of redundancy is impractical even for a single ecosystem (Gitay et al., 1996).

In addition to the direct market value of novel MNPs as oncology medicines presented in this study, a holistic account of the economic value of MNPs must also account for the economic impact of other direct, indirect and induced market effects, as well as non-market (social) values (Nijkamp et al., 2008). Direct effects include economic activities generated by the pharmaceutical industry itself (e.g. employment). Indirect effects encompass the economic impact that drug discovery will have on the suppliers to the pharmaceutical industry. Induced effects capture the economic impact of spending by suppliers of inputs to the pharmaceutical industry and those directly employed in the industry. The social value of new oncology drugs includes the economic benefits attained via reductions in mortality and morbidity associated with new treatments, likely a substantial dimension of economic value given the 10.9 million new cancer cases per year worldwide (Parkin et al., 2005). Notably, the inclusion of the social value of natural products can significantly increase economic value estimates and yield important differences in the overall valuation of a given ecosystem service (Craft and Simpson, 2001; Costello and Ward, 2006). Finally, harvesting marine organisms for MNPs may inhibit other economic values from being realized. For example, marine organisms may also have gastronomic interest (i.e., edible species) or represent a source of existence value as emblematic species that increase the public's willingness to pay for conservation initiatives and recreational usage. Thus, a more comprehensive view of the economic value of the sea for pharmaceutical research should also consider that the best use for a particular unit of biodiversity might lie outside extractive direct use for drug discovery.

The market value of marine biodiversity for anti-cancer drug discovery reported herein represents a baseline estimate of the pharmaceutical value of the sea and is presented as an at-risk value. Regardless of the complex issues surrounding the extraction and realization of this value (Li and Vederas, 2009), the simple and pressing issue is that the loss of natural resources tied to biodiversity is permanent. Currently, the repository of new pharmaceutical medicines from the sea and their underlying biosynthetic genes are threatened by increasing anthropogenic stressors and global climate shifts that affect the livelihood and diversity of marine organisms. A 2 °C increase in seawater temperature predicted by future climate change regimes may result in 15–40% of species brought to the brink of extinction (Stern, 2007). According to our valuation model, a 20% biodiversity loss equates to a market value loss of US$112 billion–1.14 trillion. Moreover, this forfeiture accounts only for anti-cancer medicines, not other biomedical applications of MNPs. The current rate of habitat and biodiversity decline is sure to disrupt ecosystem functions and endanger any services yielded to humanity from marine environments (Palumbi et al., 2009).

Ecosystem service valuation aims to first demonstrate the existence of sufficient biodiversity value to promote conservation initiates, and second, to show how to capture and appropriate enough of the value to compensate for the opportunity costs of conservation in specific areas (Simpson, 2007). The present study fulfils the former of these goals and promotes progression towards the second, where further studies focusing on case-specific scenarios and context-dependent variables will allow for the evaluation of ecosystem usage alternatives. Further, enumerating the multitude and magnitude of services that can be derived from intact ecosystems, including the pharmaceutical value of marine biodiversity, can expand society's appreciation of marine resources. Indeed, the success of conservation initiatives hinges more on the education of society, their awareness of conservation benefits and their resulting attitude toward nature, than on prospective interventions by private businesses to temporarily preserve habitats as a means to capitalize on ecosystem service value. Therefore, the application of valuation models to marine ecosystem services attempts to elucidate the true cost of habitat degradation to society and highlights the pressing need for biodiversity conservation and environmental protection.

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at doi:10.1016/j.ecolecon.2010.09.030.

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